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Vital Organ Transplant Centres

Guidelines

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REPORT OF THE SUBCOMMITTEE
ON INSTITUTIONAL PROGRAM GUIDELINES

GUIDELINES FOR ESTABLISHING STANDARDS
FOR SPECIAL SERVICES IN HOSPITALS

VITAL ORGAN TRANSPLANT CENTRES

Health Services Directorate
Health Services and Promotion Directorate

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NOTE

The information contained in these guidelines is considered current as of the date of their approval; however, since many aspects of health care and health technology are constantly changing, we welcome any suggested amendments. Information on new developments or related issues should be directed to:

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Further copies of these guidelines in either English or French can be obtained from the above address.

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TABLE OF CONTENTS

	PAGE
PREFACE	ix
LIST OF PARTICIPANTS	xiii
INTRODUCTION	1
GENERAL CONSIDERATIONS RELEVANT TO ALL TRANSPLANTATION	7
1. Organization and Coordination of Provincial Transplant Programs	7
2. Patient Load	9
3. Inpatient Bed Requirements	9
4. Inpatient Non-Bed Requirements	10
5. Out-patient Requirements	10
6. Program Allocation	10
7. Program Relationships	15
8. Organization and Policies	16
9. Personnel Requirements	18
10. Pediatric Considerations	21
11. Post-Discharge Considerations	22
12. Information Considerations: Data Collection and Sharing	23
13. Legislative Considerations	25
KIDNEY TRANSPLANTATION	
Preamble	27
1. Patient Load	29

PAGE

2. Inpatient Bed Requirements 30

3. Inpatient Non-bed Requirements 30

4. Out-patient Requirements 31

5. Program Allocation 32

6. Program Relationships 32

7. Organization and Policies 35

8. Personnel Requirements 35

9. Equipment 38

10. Space Allocation and Special Design Features 38

11. Pediatric Considerations 38

12. Post-Discharge Considerations 39

BONE MARROW TRANSPLANTATION

Preamble 41

1. Patient Load 43

2. Inpatient Bed Requirements 43

3. Inpatient Non-bed Requirements 43

4. Out-patient Requirements 46

5. Program Allocation 46

6. Program Relationships 46

7. Organization and Policies 47

8. Personnel Requirements 47

9. Equipment 49

PAGE

10. Space Allocation and Special Design Features 49

11. Pediatric Considerations 50

12. Information Considerations 51

HEART AND HEART/LUNG TRANSPLANTATION

Preamble 53

1. Patient Load 55

2. Inpatient Bed Requirements 56

3. Inpatient Non-Bed Requirements 58

4. Out-patient Requirements 58

5. Program Allocation 59

6. Program Relationships 59

7. Organization and Policies 60

8. Personnel Requirements 61

9. Equipment 63

10. Space Allocation and Special Design Features 63

11. Pediatric Considerations 64

LUNG TRANSPLANTATION

Preamble 67

1. Patient Load 69

2. Inpatient Bed Requirements 69

PAGE

3. Inpatient Non-Bed Requirements 69

4. Out-patient Requirements 69

5. Program Allocation 70

6. Program Relationships 70

7. Organization and Policies 70

8. Staffing Considerations 70

9. Equipment 70

10. Space Allocation and Special Design Features 70

11. Pediatric Considerations 70

LIVER TRANSPLANTATION

Preamble 71

1. Patient Load 73

2. Inpatient Bed Requirements 73

3. Inpatient Non-bed Requirements 73

4. Out-patient Requirements 74

5. Program Allocation 75

6. Program Relationships 75

7. Organization and Policies 76

8. Personnel Requirements 77

9. Equipment 78

10. Space Allocation and Special Design Features 78

PAGE

11. Pediatric Considerations 79

PANCREAS TRANSPLANTATION

Preamble 81

1. Patient Load 83

2. Inpatient Bed Requirements 83

3. Inpatient Non-bed Requirements 83

4. Out-patient Requirements 83

5. Program Allocation 84

6. Program Relationships 84

7. Organization and Policies 84

8. Personnel Requirements 85

9. Equipment 85

10. Space Allocation and Special Design Features 86

GLOSSARY 87

ANNEXES:

A. An Introduction to Transplantation Concepts and Terms 91

B. Organ Preservation 101

C. Special Policies Related to Transplantation 105

D. Administrative Organization, Policies and Procedures 107

E. Guidelines for Special Services 113

PREFACE

Technological advancement and changes in the delivery of health care services have led to the need for guidelines to assist in planning and implementing institutional programs and services. The guidelines that follow represent one of a series of publications produced under the direction of the Subcommittee on Institutional Program Guidelines. They provide a consistent definition of the requirements for a number of special care units, services and programs in health institutions (hereafter in the introduction referred to as services).

In general, guidelines are based on information, knowledge, experience, research and expert opinion from health professionals and organizations throughout Canada. Additional material is often obtained from national and international health organizations and from other experts knowledgeable in the subject matter. By this method, many Canadians from across the country have contributed to the guidelines and a consensus on the suggested approach has been achieved.

Background

Under the direction of the Federal/Provincial Advisory Committee on Institutional and Medical Services, the guidelines program has been in operation since 1972. A standing Subcommittee of the Advisory Committee, the Subcommittee on Institutional Program Guidelines, composed of federal and provincial government and professional representatives, coordinates the development of the guidelines commissioned by the Advisory Committee.

The guidelines are produced by the expert working groups of health professionals, some of whom are government representatives. The final draft is reviewed and recommended by the Subcommittee for approval by the Advisory Committee.

Purpose

The purpose of the guidelines is to provide a comprehensive outline of requirements for services in health institutions. While a consensus of expert knowledge and experience is reflected in the guidelines, they should not be regarded as rigid standards. Provincial health authorities may modify the application of the guidelines to meet their needs.

Where development of a service is being contemplated, we believe the guidelines will be of help in determining the need for such a service, either locally, regionally or in some cases provincially or interprovincially.

A review of established services may take advantage of the guidelines in screening deficiencies and solving problems without the need to develop new services. Where a service already exists, the guidelines will help:

- to identify problems related to administration, personnel, equipment and facilities,

- to determine necessary remedial action,

- to set priorities for corrective measures on the basis of clinical need, funding and the degree to which the service is deficient.

Future

The dramatic increase in the number of intensive and special care services in health institutions has given rise to the need for additional facilities, specialized equipment, and highly-trained personnel. At the same time, new approaches to patient care have evolved that emphasize the need for a continuum of care in which admission to an institution is only one aspect of total care. Therefore, linkages along the health care continuum, ranging from illness prevention to chronic care, must be identified. As

new treatments and procedures are put into practice, there will be a continuing need for guidelines to assist those involved in the planning and operation of institutional services.

Revisions

Due to the rapidly changing nature of health care delivery, guidelines will need regular updating and revision. The Subcommittee on Institutional Program Guidelines plans and oversees these revisions.

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INTRODUCTION

Transplantation of organs and tissues is one successful therapeutic modality in the treatment of many end stage diseases. Organ transplantation frequently achieves better survival rates than alternative treatments while at the same time providing reasonable quality of life. The five-year survival rates for liver, kidney and heart transplant patients are all better than 50 per cent. This compares favourably with the treatment of many forms of cancer. Althrough various new techniques have brought about incremental improvements, one significant factor in the improvement in graft survival has been the introduction of the new immunosuppressive compound cyclosporine.

Transplantation offers certain terminally ill patients at least a chance of life and offers chronically disabled patients a possible return to a more productive life. As survival rates improve, many hospitals are evaluating the desirability and feasibility of beginning or expanding a vital organ transplant program.

With the exception of kidney transplantation, the types of transplantation considered in these guidelines either have been accepted only very recently as established therapies or are still considered experimental. However, the pace of change is high. Predictions of the ultimate utility and number of each type of transplant can only be rough estimates. For example, indications for kidney transplantation have changed considerably over the past twenty years. The number of contraindications to transplantation has dropped to the point where there are very few absolute contraindications. This has led to a steady increase in the number of patients receiving kidney transplants. A similar pattern of expanding indications/decreasing contraindications will continue to happen for heart, liver and bone marrow transplants. The indications for marrow transplants are expanding, and further increases - e.g. for

solid tumor therapy - can be expected. The future of heart/lung, lung and pancreas transplants is less clear.

Three examples of recent of expected changes that may alter transplantation follow:

1. Cyclosporine has changed the organ survival rate and has reduced host-organ rejection, resulting in an increased success rate for cadaveric kidney transplant procedures. The long-term effects of cyclosporine are not clear at this time. Experience with cyclosporine has suggested some adverse effects on kidney function and an increased incidence of lymphoproliferative disorders. This drug is best handled by specialists in its use.

2. There has been a recent increased demand for the development of transplantation programs. Physicians have become more aware of the option of transplantation for patients who have end stage heart and liver disease. The criteria for the selection of transplant recipients have evolved such that age and many other limiting factors are no longer important. All of these have resulted in more patients being referred to established transplant programs in centers outside of Canada and to the few that are established in Canada.

3. Improved techniques for closer matching of donors and recipients now offer an opportunity to further reduce rejection of the transplanted organ.

Table 1 demonstrates the projected demand for different vital organs by the year 1990. In all cases the estimated demand is well above the current number of transplants, particularly for liver and heart transplants being done in Canada. Transplant centers in Canada should be planned with these targets in mind, even if their attainment occurs after 1990.

The need for vital organ transplant center guidelines became apparent with the realization that many hospitals engaged in kidney transplant programs may have the medical and technical expertise and the network of supportive departments necessary to implement transplant surgery programs in all specialties (heart, liver, kidney, bone marrow, pancreas, etc.). However, the resources required to operate transplant centers where either a single organ or multiple organs are being transplanted are considerable. Among the resources in limited supply are surgeons and physicians experienced in organ transplantation and the shortage of training centres. A rationalization and regionalization of these programs is considered essential.

For the purposes of these guidelines, heart, liver kidney and bone marrow transplants are considered non-experimental and pancreas, lung, and heart/lung are considered experimental. Some of these may be supplanted by technical developments. For example, whole organ pancreatic transplants may be eliminated by techniques of implantation of islet cells.

Research in transplantation has a history now approaching one hundred years. Organ transplantation, however, is viewed as a phenomenon of the last two decades. People and processes are needed to translate the innovations and advances of research into treatments at the bedside. Successful innovations seem more a burden than a boon to health service planners forced to find the money to pay for them. Processes for handling the innovations must be incorporated into the health service planning structure.

Scientific discoveries cannot be anticipated, but once made, an efficient arrangement for their development and testing is needed. As health care insurance agencies become more insistent about the demonstration of the clinical utility and/or cost effectiveness of a new procedure or drug, they must insist that mechanisms be available for testing these new procedures or drugs.

The purpose of these guidelines is to provide basic information necessary for the establishment of a vital organ transplant centre. This should insure that new centres meet minimum standards for clinical care and that established transplant centres maintain acceptable standards. The guidelines should also enable cost-effective decisions to be made, help provide transplantation facilities to all parts of the country and ensure rapid deployment of new medical advances for the benefit of Canadian patients.

It is appropriate that a health services research group be established in each transplant center to access medical innovations for potential application, initiate the appropriate pilot studies and/or controlled clinical trials, assess the costs, benefits and effects on provision of health care services and evaluate the effectiveness of the innovation at regular intervals after its introduction.

In addition to and complementing this research capability, there is a need for a national data gathering capability, to establish an information system to meet the needs of health systems planners and health care providers, plus a national coordination capability to address the problems of scarce organs or difficult organ matching problems. These are more completely discussed in the following section.

TABLE 1

PROJECTED NUMBER OF TRANSPLANTS IN CANADA PER ANNUM BY 1990

Province or Territory	Population (1990) (10^6)	Renal	Heart & Heart/Lung	Bone Marrow	Liver
Newfoundland	0.60	27	11	12	5
Nova Scotia	0.90	40	16	18	7
Prince Edward Island	0.13	6	2	3	1
New Brunswick	0.75	34	13	15	6
Quebec	7.08	320	128	142	57
Ontario	10.36	465	186	207	83
Manitoba	1.12	50	20	22	9
Saskatchewan	0.97	43	17	19	8
Alberta	2.48	111	45	50	20
British Columbia	3.26	147	59	65	26
Territories	0.1	5	2	2	1
CANADA	27.75	1248	499	555	223
Transplants carried out in Canada in 1985		737	48	151	36
Rate per Million: 1990 Projected		45	18	20	8
Ratio, Adult:Paediatric		15:1	20:1	1.5:1	5:1

NOTES

1 - Statistics Canada, "Population Projections for Canada and the Provinces, 1976-2001, Projections Catalogue, February 1979, 91-520 Occasional.

GENERAL CONSIDERATIONS RELEVANT TO ALL TRANSPLANTATION

1.0 ORGANIZATION AND COORDINATION OF PROVINCIAL TRANSPLANT PROGRAMS

Patients with end-stage organ failure who are candidates for organ transplantation differ from those with other life-threatening illnesses in that a solution to their problem, i.e. a donor organ, may depend on activities and programs in other parts of the country or even outside the country.

Like other high technology programs organ transplantation can only be performed in a limited number of institutions, often far removed from the patient's home. Because of the uncertainty of organ availability patients may be required to move to a city where such programs now exist and/or arrange for rapid transportation or paging systems so that they will not miss an opportunity if it arises.

Unlike other high technology programs in which treatment can be booked on an elective basis, the majority of transplant candidates must wait for a commodity in short and uncertain supply and of unknown and unreliable quality. Changes in neurosurgical procedures, legislative changes (e.g. seat belt legislation and legislation related to protective helmets) and other factors may further affect donor availability. In the meantime the quality of their lives may deteriorate and in the case of cardiac and liver recipients life may end before a suitable donor organ is found.[1]

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[1] This guideline should be read in conjunction with the guideline on Organ and Tissue Donation Services in Hospitals, Institutional and Professional Services, Health Services Directorate, Health Services and Promotion Branch, Department of National Health and Welfare, Ottawa, 1986.

To minimize these problems, effective organization for both the provision and integration of transplant services and organ donation systems must be established. In the heavily populated regions of Canada, this can be accomplished for most organs on a provincial basis. For the less populated parts of the country, interprovincial arrangements are desirable. Indeed, because of the scarcity of heart, lung and liver donors, a national organ distribution system with international linkages is necessary; it also may be desirable for the ever increasing proportion of pre-sensitized kidney transplant patients.

This may require the setting up of national tissue typing and organ distribution programs. It is recognized that the necessity for such arrangements will change as advances in transplantation occur. On the other hand, it is anticipated that such national organizations, once in place, will continue to have significant problem-solving roles.

Consideration should also be given to the system for providing, controlling and ordering cyclosporine and other immunosuppressives, particularly for patients who have been transplanted outside of their home province.

The concept of regionalization of certain hospital procedures is supported by studies demonstrating correlations between mortality and surgical rates, but the data do not include transplantation. For a comparison of low and high volume transplantation centers to be valid, a number of factors such as selection criteria, risk factors, timing of surgery in the progression of the disease, etc., would have to standardized. At this point opinion is varied, some argue that high volumes and specialization translate into improved survival, others argue that "quality" is not dependent on quantity provided a minimum number of transplants are performed. The National Institutes of Health (NIH) Consensus Development Conference concluded that for liver transplantation

to gain its full therapeutic potential, expansion of this technology should be restricted to a limited number of centers.

2. PATIENT LOAD

The rate of kidney transplantation is projected to be 45 per million population per year by 1990. The best rates so far achieved is 55 per million per year in Austria. For cadaver kidney transplantation, (15 per cent are living related donors) the best current and the optimal projected rates are 35 and 39 per million respectively. Since almost all organ donors are at least kidney donors, the maximum achievable rates for other organs will be less and usually substantially less than that for kidneys, unless there is a radical and unforeseeable change in the availability of donors. The projected 1990 rates for various organs are outlined in Table 1. The restricted availability of donors implies that only a limited number of multi-organ transplant programs can be justified with an approximate population base of 2.5 million for each. It must be emphasized that donor organ availability is the ultimate limiting factor in this sequence.

Giving the present population distribution in Canada, this implies that there should be at least one such multi-organ centre in British Columbia, one each in Alberta and Manitoba, three to four in Ontario, three in Quebec and one in the Atlantic Provinces. This will require interprovincial negotiations and organizations.

3. INPATIENT BED REQUIREMENTS

Table 2 outlines the bed requirements for the different organ transplantation programs. Details regarding these bed requirements may be found in

the individual sections. Planners should note, however, that beds will have to be allocated for transplanted patients during the years following their transplants, for follow-up care and for terminal care, as the patients are likely to continue to return to the same hospitals until they die of any causes.

4. IN-PATIENT NON-BED REQUIREMENTS

The development of transplantation programs requires technical expertise and a full range of supportive services. Some of the requirements are indicated in Tables 2 et 3, and described in more detail in the sections related to individual organs.

5. OUT-PATIENT REQUIREMENTS

As discharged transplant patients require life-long monitoring and follow-up, particularly for their cyclosporine levels, outpatient facilities are required. Many of these patients travel considerable distances. Consideration should be given to the availability of hostel or other patient accomodation services near the hospital.

6. PROGRAM ALLOCATION

Transplant centers should be based in teaching hospitals where critical care capabilities are at the highest level and medical staff are devoted to the organ failure program full time, providing medical coverage in-house 24 hours a day. Where there are (a) access to a well developed immunological service, (b) an active end stage organ failure program conducting major surgery on the organ in question, (c) the appropriate physical and manpower resources for transplantation, the establishment of a transplant program may not require extensive further training or expenditures.

For example, where there already exists a kidney transplant program, appropriate immunological and laboratory services, and an active cardiac surgery

program, (with open heart surgery and heart/lung bypass capability) a cardiac transplant program could be reasonably developed.

In the absence of the full range of necessary backup services the initiation of a transplantation service should not be undertaken. In addition, the potential number of transplants must be considered in determining the location of a transplant service. While minimal numbers are not generally consistent with high levels of expertise, transplantation programs should only be established where it can be anticipated that the effective minimum patient load can be achieved (Table 2). It must be recognized that the procedures of transplantation and the general demands of end stage organ failure programs can cause disruptions to the other programs and services in a hospital.

TABLE 2

TRANSPLANTATION BED REQUIREMENTS AT EFFECTIVE ANNUAL MINIMUM LOAD

PATIENT LOAD & BEDS	Kidney	Heart & Heart/Lung	Pancreas	Bone Marrow	Liver
Effective Minimun Annual Patient Load*	45	50 & 10	12	40	25
Workup Beds	occ.	11	**	0.4	4
U.C.U. Beds	occ.	5	**	1	1
Isolation Beds	0	0	0	4	0
Post-op Ward Beds	5	6	**	4	4
NOTES:					
* Minimum Start-up Load	20	10 & 3	3	12	12
** As for Renal Transplantation					

Occ. Occasional

The proximity of other transplantation centers is another factor to consider in the establishment of a transplant program. The development of a second transplant program in the same region or province, where the first program has not reached capacity, is inadvisable, even though the proposed program may have the requisite back-up services. It would be preferable for the two or more institutions involved to join forces in a coordinated regional or provincial program, with each institution complementing the services of the others. For instance, the division of the program could be age or organ specific. A phased-in approach to the development of additional programs or centers is suggested.

The extent to which program success is related to a high number of transplants is controversial and conclusive studies are not available. In several there is a negative correlation between patient mortality and surgical rates. This supports the concept of requiring minimum numbers of transplants per year per centre (Table 2) to achieve and maintain technical expertise. Regionalization of services is one way of attaining this end.

Another factor to be considered in the development of a vital organ transplantation program is the issue of single versus multi-organ transplant centers. There can be no question that there are some advantages associated with multi-organ transplant centers, particularly for the sharing of immunology and laboratory services. With the exception of bone marrow transplantation, the immunological problems are fairly similar for all vital organs. Similarly, specialty laboratory services such as cyclosporine assay are common requirements. The presence of an experienced kidney transplant team aids in the establishment of a second transplant program, such as liver or heart. Organ donation systems are also common for organ transplant programs.

TABLE 3

TRANSPLANTATION IN-PATIENT NON-BED REQUIREMENTS

SERVICES	Kidney	Heart & Heart/Lung	Pancreas	Bone Marrow	Liver
MEDICAL SPECIALTIES					
Anaesthesia	+++	+++	+++	+++	+++
Cardiology	++	+++	+++	++	++
Cardiovascular/ Thoracic Surgery	+	+++	+	+	++
Diabetology	+++	++	+++	0	+
Gastroenterology	++	++	++	+++	++
General Surgery	++	++	++	++	+++
Hematology/Oncology	++	+++	+++	+++	+++
Infectious Disease	+++	+++	+++	+++	+++
Nephrology/Dialysis	+++	++	+++	+	++
Neurology	+	+	+	+	++
Ophtalmology	++	+	++	++	+
Organ Donation Team	+++	+++	+++	0	+++
Psychiatry	+	+	+	+	++
Pulmonary Medicine	+	+++	+	+++	+++
Urology	+++	+	+++	+	+++
DIAGNOSTIC IMAGING SERVICES					
- Cardiac Cath. Lab.	+	+++	++	0	+
- Computed Tomography	+	+++	+	+++	+++
- Nuclear Medicine	+++	+++	+++	+	+++
- Radiology	+++	+++	+++	+++	+++
- Ultrasound	+++	+++	+++	++	+++
SPECIAL LABORATORY SERVICES					
- Immunosuppresant Monitoring	+++	+++	+++	+++	+++
- Microbiology/ Virology	+++	+++	+++	+++	+++
- Special Histology	+++	+++	+++	+++	+++
- Tissue Typing	+++	+++	+++	+++	+++
- Transfusion Service	++	+++	+++	+++	+++
OTHER SPECIALTIES AND PROFESSIONAL SERVICES					
Chaplaincy	+	+++	++	+	+++
Dentistry	+	+++	+	+++	++
Pharmacy (incl. T.P.N.)	+++	+++	+++	+++	++
Physiatry/physiotherapy	+	+++	++	+++	++
Social Services	++	+++	++	+++	++
Therapeutic Radiation	0	0	0	+++	0

LEGEND

+++ Core, Essential

++ Necessary and must be Readily Available

\+ Occasional Consultations Desirable

0 Not Required

TABLE 4

TRANSPLANTATION BLOOD AND BLOOD PRODUCT REQUIREMENTS PER ORGAN

BLOOD PRODUCT REQUIREMENTS	Kidney	Heart and Heart/Lung	Pancreas	Bone Marrow	Liver
Units of Blood within 24 hours of Procedure	1 - 2	6 - 15	**	1 - 2	35
Total Units of Blood (for one year)	5	20	**	8 - 30	40
Blood Products: (plasma, cryoprecipitates, Albumen, platelets, etc.)	low	high	**	high	high

** As for renal transplantation.

When more than one center in a region is involved in providing multi-organ transplantation services, inter-institutional cooperation should be established, to take advantage of complementary support services. Ideally, a single center will be able to provide multi-organ transplantation services, with all of the necessary support services, for an entire region.

7. PROGRAM RELATIONSHIPS

Specific information on this subject is contained in the individual guidelines. In general, however, each transplantation modality has program relations with the programs providing conventional therapy to patients who may be screened for or awaiting transplantation, with other transplantation services in a multi-organ transplant centre, with other transplantation programs in the region or province where they exist and with the regional organ donation programs.

8. ORGANIZATION AND POLICIES

8.1 General Organization

A vital organ transplantation program cuts across many clinical departments and services, making a systematic management approach necessary. Only with a committed and inter-disciplinary team of professionals will the program become cost-effective and not make unrealistic demands on the resources of the host hospital.

Specific information is contained in the individual sections of this guideline. Annexes C and D outline policies which pertain to all transplantation.

8.2 Policies and Procedures

Policies and procedures should be prepared in the form of a manual and should be readily available to the staff of the center. Transplantation is developing at such a pace that special policies should be reviewed and update annually. All experimental therapies should take the form of approved protocols, with appropriate consent forms and ethics committee approval.

An interdisciplinary advisory committee of personnel involved with the transplant program from administration, the medical specialties concerned, including immunology, nursing and other heavily involved hospital units should be developed.

Transplantation is an emergency procedure. Elective cases that are cancelled because of a transplant procedure should be rebooked the same evening or the following day to minimize the disruption of the regularly scheduled cases. The transplant program should not be in competition with routine surgery but should complement the surgical program for the organs concerned.

Excellent communication must be established with the media to promote the education of other physicians

and the public on the benefits of transplantation and the need for organ donation.

The use of immunosuppressive agents which have not been released by the Health Protection Branch (H.P.B.), Health and Welfare Canada, for use in solid organ transplantation, such as anti-lymphocyte globulin (ALG), should confrom to the restrictions placed on investigational new drugs. An identified investigator in charge of the distribution of such drugs is required.

The use of experimental drugs on an emergency basis is properly undertaken outside of the above situations only with an emergency drug release from H.P.B.

8.3 Quality Assurance

Quality assurance is supported by the analysis of patient and graft survival and graft function. Ideally, such data should be collected locally (see Section 10 below), with appropriate data submitted to a national transplantation data base (e.g. the Renal Failure Register). Mortality should be reviewed, preferably in the setting of medical or surgical rounds. Adverse drug reactions must be observed and recorded. One good method for monitoring quality is by engaging in research, involving several centers, with results compared between centers. Moreover, research is necessary to improve outcomes and develop new agents or new uses or combinations of old therapies. The research projects can monitor graft/patient survival, organ function, complications, etc. Such projects may evaluate therapeutic agents (e.g. monoclonal antibodies), organ preservation, donor parameters (e.g. effects of donor age), surgical technique, psychosocial parameters, etc.

Analyses should be done with data analyzed by a qualified statistician using a computer with modern statistical programs. As much as possible, however, major policies or therapeutic strategies should be based on results of randomized prospective trials of appropriate size. A statistician, methodologist or

clinical epidemiologist is essential in planning such activities.

Epidemiology: organ transplantation should be seen as part of the end stage organ disease support process, and should contribute data to be used for defining the patient population, results and requirements for such treatments. At present, one example of such activities is the Canadian Renal Failure Registry. Such efforts are essential to project the resources required.

9. PERSONNEL REQUIREMENTS

9.1 Medical Staff

Each organ section of this guideline outlines the medical staff requirements for that modality. However, it should be noted that all transplantation services require 24-hour medical coverage within the hospital, irrespective of whether the hospital has a postgraduate teaching program in the specialties concerned.

9.2 Nursing Staff

Pre-operative Ward Staff

In the preoperative assessment phase, nursing staff must be knowledgeable and skilled in the management of individuals with other diseases of the organ under consideration.

Pre-operative and Post-operative ICU Staff

The critically ill organ recipient candidates in some instances will await a donor organ in an intensive care unit. The nursing staff caring for the recipient must be able to integrate and apply a broad knowledge base to complex patient problems.

Operating Room Staff

For setting up of a new program, on-site experience in an established transplant center or skill training

in an experimental laboratory setting is essential. Operating room staff must be familiar with the techniques and the equipement involved with both donor organ procurement and the recipient transplantation procedures.

Post-operative Ward Staff

Nurses must have medical and surgical nursing skills to care for patients following major organ surgery. The nursing unit requires staff with expertise in both disciplines. Ward nurses must be capable of teaching the patient and family about the medications, including dosage, timing of administration, purpose and potential complications. The nurses play a major role in patient and family teaching prior to discharge and during follow-up care in the outpatient clinic. The teaching role may be undertaken by the outpatient department nurses or the transplant patient coordinator.

9.3 Transplant Patient Coordination

Frequently a person is designated to coordinate all activities which facilitate the care of patients and the flow of information through the transplant process. Either a nurse or a person with another suitable background may be assigned to coordinate these activities. In other cases these duties can be performed by existing personnel, including staff physicians, house staff residents, secretaries and clerks, or may be combined with the duties of the organ donation coordinator. The responsibilities can include part or all of the coordination of:

- work-up of the potential transplant recipients,
- work-up of the living related kidney donor,
- fielding donor calls,
- donor/recipient matching,
- operating room bookings for the donor and the recipient,
- donor specific transfusions,
- the transplant follow-up clinic, including scheduling visits,

- booking and follow-up of results of special laboratory study and imaging,
- cyclosporine blood level testing and reaction to results,
- monitoring of patient compliance,
- collecting and disseminating pertinent information,
- the activities of the clerical staff.
- involvement with public relations activities and patient and family education.

The office of the transplant patient coordinator should be linked with the organ donation system, with its attached public relations and data collection functions. Under certain circumstances these coordinator functions may be assigned to various other individuals, such as a secretary to the Program Director.

The amount of time required for these functions will depend on the number of transplants performed per year. One estimate is that one coordinator should be available per 30 new kidney transplants per year. Two may be required for 50 heart and 10 heart/lung transplantation procedures annually. The number of stable transplants being followed as out-patients would also affect the requirements for coordinators. In some units it may be feasible to have the dialysis coordinator and the transplant patient coordinator position combined into one position. However, in larger units it will be necessary to have separate individuals for each of these roles.

Due to the complexities and cost of multi-organ transplantation, it may also be helpful to have a dedicated administrative individual who could facilitate the solving of logistical and financial problems. Accounting will involve costs incurred in institutions located outside the province or country. This individual would be accountable to the Program Director and the administration of the Hospital. This individual's role would be that of a facilitator to meet the needs of the program.

9.4 Staff Training and Qualifications

Training in the medical and surgical aspects of organ transplantation is not formally available in Canada. Indeed, the majority of Canadian transplanters trained abroad or learned "on the job". In view of Canada's pre-eminence in the field of transplantation, the establishment of training programs and positions is an essential part of the evolution of this treatment modality within the country.

The very nature of the endeavor implies that it must be a postgraduate, i.e., a post fellowship activity, funds for which are a scarce commodity in Canada. Steps to rectifying this situation are urgently required.

New programs should not be started without a core of experienced and committed medical and surgical personnel. It is advisable that a new program be started in liaison with an existing program, from which it can derive ongoing support and consultation, and to which it can refer problems which are beyond its capability. Appropriate orientation and teaching for house staff will be required, including the theoretical background as well as clinical practice.

The appropriate staff training and educational programs should be established for all categories of the health care team. The program should be based on clearly defined learning objectives. Continuing staff education should be based on identified learning needs and should keep pace with advances in medical and technological aspects of transplantation. In addition, transplantation issues should be discussed at grand rounds, so that the consultants also acquire some familiarity with the philosophies and practices of transplantation.

10. PEDIATRIC CONSIDERATIONS

In the development of a vital organ transplantation program, the ability to provide a service to children as well as adults is affected by two major, but con-

tradictory considerations. On the one hand, the desire to meet the special care requirements of children, argues for surgery taking place within a pediatric institution. On the other hand, the need for special skills in the surgery and in the management of the post-operative course come only with the higher volumes occurring in adult centers. It is, of course, possible for the surgical/transplant team to work in two different institutions. Circumstances will vary, and where volumes are high enough to maintain skills, the pediatric programs may properly be located in pediatric institutions. Factors to consider will vary with the type of organ involved, and will include traval, time and distance. In other regions, cooperation between adult and pediatric institutions should allow policies and protocols to be established which either allow the transplant team to work in both adult and pediatric institutions or enable children to be properly cared for in an adult-care hospital.

11. POST-DISCHARGE CONSIDERATIONS

In setting up a program, the importance of follow-up is often underestimated. Patients who do not attend follow-up appointments have a high tendency to fail to take their medications regularly. Compliance is of critical importance. The outpatient clinic and the transplant office are the key elements to long-term follow-up.

Transplant centres can only be located in large institutions, usually in large cities. This means that many patients will have to travel long distances to the transplant centre. Accomodations close to the transplant centre will be required for each patient's family during the time that the recipient is in hospital, and for the recipient and family during the post-transplant period of surveillance and support, including outpatients from remote sites.

In addition, the centre must communicate with the patient's private physician, whether locally or at a distant centre. These communications are particularly important for patients who live at a distance from

the transplant centre and for whom non-transplant physicians must provide the bulk of their ongoing care.

The family physician, internist or surgeon in a remote area can assume responsibility for week-to-week decision-making in stable patients beyond the first few months and particularly beyond the first year. Regular telephone contact with transplant centre specialists is necessary, as one cannot expect the local physician to know all of the details of the management of the transplant recipient. The local physician must be supported and encouraged to call the transplant director or the transplant patient coordinator.

Attending physicians remote from transplant centers may benefit from an information sheet describing a few key management points about cyclosporine and other medications particularly about interactions with commonly used drugs such as erythromycin or non-steroidal anti-inflammatory drugs.

12. INFORMATION CONSIDERATIONS: DATA COLLECTION AND SHARING

It is necessary to have accurate and up-to-date information within individual programs, interprovincial organ sharing organizations and provincial, national and international agencies concerned with transplantation. National clinical guidelines within Canada are particularly germane and can only be achieved by the setting up of national information systems which must include not only demographic and end result reporting but also the capability of interprogram comparisons, national clinical trials and multivariate analysis of the data collected.

The basic functions to be served by a data system are:

1. To provide a register of patients awaiting transplantation or who have been transplanted.

2. To serve as a transplant waiting list, indicating the number of patients waiting for a particular organ and the waiting time. An expanded system could act as an on-line list to allow organ matching and exchange.

3. To act as a register of all vital organ transplant procedures carried out in Canada or on Canadians outside Canada.

4. To record outcomes for patients on the transplant waiting lists and of the transplants themselves, to permit evaluation of the organ failure programs.

5. While costs cannot be specifically recorded on each patient, some analysis of cost effectiveness may be possible by means of program costing in each transplant centre.

Essential to the functioning of a unit, where research and good patient care are closely interrelated, are facilities for accurate data collection and analysis. A flow sheet should be maintained on each patient on which are recorded clinical and laboratory data and therapy, updated daily on each inpatient and after each clinic visit on each outpatient. This can be a conventional or computerized flow sheet. If it is computerized, a hard copy should be accessible at off hours or when the system is down. Appropriate data should be submitted to the organ distribution centre, the tissue typing laboratory and the national and international registries.

Data collection should be computer-based and shared with sister institutions to ensure the optimum standards of care and research and to facilitate the exchange of information relevant to transplantation. Programs for the sharing of information on donors and recipients are required to assure equal access to quality care throughout Canada.

13. LEGISLATIVE CONSIDERATIONS

Legislation should be enacted to ensure optimal multi-organ usage, to stimulate and protect treating physicians involved with the referral of the donor for organ transplantation, and donor management by the transplantation team following the declaration of brain death in order to ensure optimal organ function until the time of and immediately after transplantation.

Legislation must ensure the rights of acceptance as a candidate for transplantation, the rights of the recipients to be involved with or to decline involvement with experimental studies, to ensure access to and full support by area social service and medical facilities and funding for all aspects of the transplantation program.

KIDNEY TRANSPLANTATION[2]

PREAMBLE

Kidney transplantation is regarded as the treatment of choice for end-stage kidney disease in children and young or middle-aged adults, at least up to age 55. The best personal survival is with a living related donor transplant with at least one haplotype match. Failing this, kidney transplantation with a kidney from a cadaver donor achieves personal survival equal to that of dialysis (adjusted for risk factors) with higher levels of personal rehabilitation. It is generally held to be more cost effective than dialysis.

A living donation of a kidney is regarded as a safe and ethically sound procedure to undertake for a consesnting adult donor. Except in unusual circumstances, living donors are first degree relatives (i.e. parents, children, or siblings of the recipient) and have at least one haplotype HLA match. With such donors, personal survival of the recipient should be virtually 100 per cent one and two years survival. Donor survival is not believed to be impaired measurably over at least two decades.

At the moment, completely unrelated living individuals, unless closely emotionally related, are not regarded as suitable donors. Emotionally related but genetically unrelated donors (close friends, spouses) have been used infrequently, but careful judgments must be made about the impact of the donation process on the personal relationship involved, and of seeking a donation and of refusal of donation by the potential donor. Such emotionally related donors as a source of kidneys are therefore to be used very

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[2] This section should be read in conjunction with the Guideline on the End-Stage Renal Disease Program, published by the Department of National Health and Welfare, Health Services and Promotion Branch, Ottawa, 1986.

judiciously. Unfortunately, over 80 per cent of dialysis patients have no such suitable, willing relative, or an acceptable emotionally related donor. Thus cadaver donors remain the main source of kidneys for transplantation.

The science of safe organ transplantation, coupled with the very high survival that is possible on dialysis, means that it is no longer acceptable for a center to be doing a small number of transplants because the physicians and surgeons cannot be committed to transplantation. Kidney transplantation should be performed by individuals who are willing to devote a considerable amount of time to the service. Thus the minimum acceptable number of transplants in order to have a viable program offering suitable patient and graft survival is rising.

Conversely, due to advances in patient management and decreasing complications, the average length of stay is lower and throughput is higher. Thus the existing units are able to accomodate more patients, and there is little need for increasing the number of kidney transplant units.

Every dialysis patient should be considered for transplantation, and have access to an identified and active kidney transplant program.

GUIDELINES[3]

1. PATIENT LOAD

Patient load will be determined by the number of donor organs and the number of recipients referred for and awaiting a transplant. Ordinarily, donor availability is the limiting factor.

The projected demand for kidney transplants per annum in 1990 in Canada is estimated to be 1248 (compared to 629 actually performed in 1985). (See Table 1, page 5.) It is sufficient to meet the demand, and for this reason this figure is used. If one assumes that: (1) about 1500 new patients will be referred for treatment of end stage kidney disease (about 60 per million); (2) about 2/3 of these will be suitable for and agreeable to kidney transplantation (1000); (3) about 250 patients willi require retransplantation per year (due to failures among new and old transplant recipients), then the figure of 1250 is a realistic planning estimate of the requirement.

However, it is likely that, due to limited donor availability, the number of kidney transplants will continue to fall below the demand in 1990.

The minimum number of kidney transplants to be undertaken by an independent program should be 20 in the first year, in order that staff skills and interests be maintained. The program should develop toward a minimum of 45 transplants per year.

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[3] This guideline must be read in conjunction with the section entitled "General Considerations", beginning on page 7.

2. INPATIENT BED REQUIREMENTS

At least 1 bed is required for every 10 transplants performed per year, and about 1 additional bed for each 50 to 100 patients being followed. (See Table 2, page 12.) The average duration of the first admission for kidney transplantation has fallen considerably in recent years. The median duration should be about two to three weeks, with some admissions as short as 8 or 9 days. The inpatient length of stay will in part depend on the availability of hostels and other accomodation arrangements for out-of-town patients and the geography of the region; therefore consideration should be given to the availability of out-of-hospital accomodation for workup prior to transplant and post-transplant care.

Patients who have vigorously rejected previous transplants often require longer stays. The principal reasons for prolonged stay are acute tubular necrosis, rejection and complications such as cytomegalovirus (CMV). In hospitals using prolonged courses of antilymphocyte globulin (AGL) or other antilymphocyte antibodies, particularly those which require indwelling central lines, admission may be necessary for the duration of the treatment. However, prolonged courses of ALG or similar antibodies (beyond 14 days) are becoming less necessary.

3. INPATIENT NON-BED REQUIREMENTS

The general requirements for an organ transplant program are outlined in Tables 3 et 4 on pages 14 and 15. On those services, the kidney transplant program requires the following to be available either within the institution or in a facility shared with an adjacent institution:

Within the Institution	Within the Region
biochemistry	cyclosporine
microbiology/virology	radioimmune assay
hematology/transfusion	CT scanner
radiology	tissue typing
diagnostic ultrasound	integrated dialysis
nuclear medicine	program
infectious disease	
consultation	
kidney pathology	

4. OUT-PATIENT REQUIREMENTS

The outpatient requirements are of 2 types: (a) pre-transplant; and (b) post-transplant.

4.1 Pre-Transplant

The period of the transplant workup is usually coordinated through the office of the transplant patient coordinator. This individual assembles a transplant medical chart before a patient is put on the list for a cadaver transplant. The transplant office may also coordinate the workup of the living donors. In the majority of cases the transplant workup is performed on dialysis patients, and must be coordinated with dialysis treatments.

4.2 Post-Transplant

The core of the post-transplant out-patient requirement is an outpatient clinic area where patients can be seen for regular follow-up visits. Regardless of the time of discharge, daily follow-up is needed in most patients for at least 4 weeks. Medical assessment must be coupled with assessments by the pharmacist, dietitian, and at times other consulting services listed under Section 3 above. Dermatology and gynecology/obstetrics follow-up may be necessary. (Dermatologic problems are particularly frequent in the immunosuppressed patients). In the immediate post-discharge period, some of these needs may be met by the inpatient unit on an ad hoc basis. The outpatient facility may be either in the

outpatient department or in a space adjacent to the end stage kidney failure inpatient facility.

The impact of the increase in outpatient activity on the biochemistry laboratory is that overall workload, including the cyclosporine radioimmune assay, will increase in proportion to the number of new kidney transplants performed. A system for performance of creatinines on a stat basis should be in place. If large batches of outpatient samples arriving from the clinic strain the capacity of its equipment and personnel, reorganization of laboratory facilities may be necessary to accomodate the load on clinic days.

5. PROGRAM ALLOCATION

The rate of referral of patients for end-stage kidney disease is approximately 55 per million in Canada. The rate of transplantation is approximately 30 per million. Assuming that the average center should perform approximately 40 transplants per year, and that few if any centers will do less than 25 per year, the target should be one center per million population, or 20 for all of Canada.

An indicated in the preamble to this section, there is little need to develop any new, independent kidney transplant program in this country before at least 1990, because of the improved results and shortened stays in existing programs.

6. PROGRAM RELATIONSHIPS

The natural relationships of the kidney transplant program are with other organ transplant programs, with immunology specialists, and with nephrology and dialysis services.

Appropriate relationships should be established among kidney transplantation centers to permit kidney distribution on an equitable, prearranged basis. A balance must be struck between keeping total preservation time short and achieving equitable distribution and good HLA matching (particularly B and D locus matching).

Other organ transplant programs should operate in concert with kidney transplantation in terms of donor selection and management, organ preservation and distribution, in-hospital services and follow-up mechanisms. The diagnoses and monitoring of rejection for all solid organs have many common aspects, and each program can benefit from the sharing of clinical experiences and resources.

The use of transplantation-style immunosuppression (pulse steroids, cyclosporine, ALG, monoclonals) will probably increase in life-threatening autoimmune disease. This provides a natural relationship between the kidney transplantation program, with its vast experience with such agents and their complications, and the non-kidney immunologic problems.

The link between nephrology and dialysis and transplantation is self-evident. The planning for transplantation should begin before dialysis, and transplantation may preempt dialysis for many patients. On the other hand, dialysis support for failing transplants must also be planned. Kidney transplantation resources are best viewed not in isolation but as a component of an integrated approach to care of the patient with kidney failure.

The principal supporting services required are the organ distribution and tissue typing services. Organ retrieval and distribution are dealt with in a separate section.

The tissue typing laboratory should be headed by a person with the appropriate experience and training in the fields of tissue typing and immunology, who can serve as a resource to the physicians and surgeons in the clinical program. This person supervises the laboratory technicians.

The most important function of the tissue typing laboratory is cross-matching. Sensitive cross-matching procedures should be used, and in some cases of doubt the results should be reviewed by the most experienced person and be interpreted so as to err on the side of protecting the patient from hyperacute

rejection. This cross-match should be regarded as having the same medicolegal significance as the cross-matching of blood. Ensuring reliability in cross-matching should be regarded as an important responsibility of the director of the tissue typing laboratory. In smaller centers where a technician for cross-matching and tissue typing may not be available 24 hours per day, it will be necessary to establish appropriate arrangements to refer off-hours testing to a larger center.

The tissue typing laboratory should screen patients on the waiting list against a panel of randomly selected individuals for the presence of cytotoxic antibodies. The presence of high levels of cytotoxic antibody, may indicate that the patient has a much lower probability of obtaining a suitable kidney, and is a useful guide to planning therapy.

The importance of matching the donor and recipient class I or class II HLA antigens has been discussed in Annex A. As a generalization, such matching is desirable but the absence of matching does not preclude excellent clinical results. Tissue typing of the donor and recipient should be performed and recorded to enable evaluation of the effects of matching in future analytical studies.

The number of technicians required for tissue typing activities will be a reflection of the number of kidney transplants done per year in that center and the number of patients on the transplant waiting list. One estimate is four full time equivalent technicians for up to 100 kidney transplants per year.

Red cell cross-matching, performed in the routine blood transfusion laboratory, is at times important in kidney transplantation, particularly in donor-specific transfusions and in transplanting patients known to have antibodies against unusual red cell antigens. Ordinarily, kidney transplantation does not constitute a problem for the blood bank, and requires little blood in the usual case.

7. ORGANIZATION AND POLICIES

7.1 Program Director

A physician or surgeon should be identified to organize and supervise the transplant program and to liaise with the dialysis program, in collaboration with other members of the transplantation team. In some centers this position may be fulfilled by the Director of the Dialysis Unit, In others a transplantation nephrologist, a committed urologist, a general surgeon or a vascular surgeon may fulfill this role. A certain amount of administrative time should be committed by this individual. The Program Director should devote the majority of his time to transplantation and related activities.

7.2 Policies and Procedures

Policies and procedures should be prepared specifically for this service. General guidelines for policies may be found on page 16 and in Annex C.

8. PERSONNEL REQUIREMENTS

8.1 Unit Director

The unit director should be trained and experienced in kidney transplantation, and can be either a nephrologist or a surgeon (a urologist or a general surgeon).

8.2 Other Medical Staff

The medical and surgical staff of a kidney transplant program must have specialist qualifications, and special training in the management of kidney transplantation. There should be both surgical and internal medicine expertise in kidney transplantation available routinely to all the patients. The available routinely to all the patients. The program must be covered 24 hours a day, seven days a week, by such staff physicians and surgeons, with appropriate on-call coverage.

Certain consulting services are important to the support of this group of patients, who often suffer from significant disease in other organ systems. These include: a) a urologist if the urologist is not the transplanting surgeon; b) nephrologists with access to all modalities of dialysis; c) an endocrinologist with special interest in diabetes, for managing the 10 per cent or more of these patients who will be end-stage diabetics (the endocrinologist should have an identifiable commitment to the kidney transplant program, and be able to follow patients in the out-patient clinic as well as seeing them daily as inpatients to manage their insulin); d) infectious disease expertise, on a 24 hour a day, seven days a week on-call basis; e) a pathologist with special interest in kidney disease.

The other consulting services frequently required include cardiology, gastroenterology, general surgery and hematology, as well as the medical imaging specialists (radiology, ultrasound, nuclear medicine).

In-house physician coverage

It is mandatory that patients undergoing such potentially complicated procedures have available an in-house physician on a round-the-clock basis. Such physicians should have training in insertion of central lines, which are mandatory for administering ALG and for CVP monitoring in the perioperative period. One possibility is a joint kidney transplant and general nephrology unit, which is a frequent model in this country, where the same physicians are on call for general nephrology, dialysis and kidney transplantation.

8.3 Nursing Staff

Some of the medications may be unfamiliar to the nurse on the medical or surgical unit. For optimal patient care in the early post-operative period, the patient should be nursed in a specialized transplant or kidney unit. Transplant centers in which the medical protocol includes hemodynamic monitoring

should designate an appropriate number of intensive care beds.

The nurse/patient ratio will depend on the number and complexity of the patients and should be established using an appropriate patient classification system. Nursing staff trained in designated added nursing skills and certified in selected, sanctioned medical acts (according to the prevailing standards of nursing practice) should care for kidney transplant patients.

Isolation procedures are not routinely required for kidney transplant recipients. In certain circumstances (e.g. hepatitis B positive patients) isolation or protective isolation facilities may be necessary, with the availability of dialysis in the same room.

8.4 Other Staff

A dietitian should be assigned to the program to teach and counsel the patient and family about dietary restrictions, to teach meal planning and preparation, budgeting and food shopping. Problems with weight control for many patients in the post-transplant period, the desirability of protein restriction in kidney insufficiency and the increased numbers of diabetics being transplanted, all contribute to the requirement for an active dietetic consulting service. The dietitian should be qualified to meet the standards of the appropriate provincial regulatory body.

Approximately one half-time equivalent social worker will be required for each 40 patients per year. The responsibilities of the social worker will depend to some extent on the job description of the kidney transplant patient coordinator. Where the coordinator is not a registered nurse, and has a minimal role in direct patient counselling and teaching, the role of the social worker will increase. In general, the social worker is required to be available on a consultation basis. The social worker can advise staff concerning patient problems, provide relevant education, and organize and coordinate community

support services. While the requirements for input by the social worker have decreased, the availability of consultataion in social work remains mandatory.

Secretarial and clerical assistance (for data collection) is necessary.

8.6 Staff Training and Qualifications

See Section 9.4 on Page 21.

9. EQUIPMENT

Kidney transplantation requires little equipment not available in the average kidney unit. The administration of ALG requires a portable pump. A cardiac arrest cart should be nearby. Emergency dialysis equipment should be available.

10. SPACE ALLOCATION AND SPECIAL DESIGN FEATURES

The immediate postoperative kidney transplant patient should be nursed in a standard single room, ideally with hemodialysis capability and a private bathroom/toilet. Beds grouped in a designated area with access to hemodialysis and to intensive care unit beds for selected transplant patients are recommended. After the first week, nursing in a two-bed room with a shared bathroom is justified. Appropriate steps for isolation should be taken when indicated. A lounge area for patients and their families is desirable.

11. PEDIATRIC CONSIDERATIONS

Very young children (five years) are now being treated for kidney failure. Results have not been as good as in older children, adolescents and adults. Such children have a higher incidence of non-immunologic kidney failure. Moreover, some impairment of kidney function which would be acceptable in adults may retard growth and development in children less than 5 years old. Until successful protocols for these children are established and

certain long term problems, such as the proper role of cyclosporine in the very young, can be evaluated, the care of very young children should be confined to specialized pediatric institutions. Older patients may be treated in an adult hospital, as appropriate.

Living donor transplantation is being used for treatment of kidney failure in children. This will require the involvement and support of an adult hospital, at least in the workup and evaluation of the living donor, and possibly in the posts-operative management.

Children with kidney failure often experience retarded growth, emotional development, sexual maturation and possibly interference with their education. As the parents are intimately involved with these problems, the development of independence often suffers. Special social and psychological support, much beyond that required by an adult, may be required, and should be planned in the organization of the program.

12. POST-DISCHARGE CONSIDERATIONS

A reasonable goal in the stable patient beyond 12 months is one visit every three months to the follow-up clinic. Transportation from remote areas may be required. In periods when close follow-up is need (e.g. post-rejection or after a serious infection), some local accomodation may be necessary for outpatients

BONE MARROW TRANSPLANTATION

PREAMBLE

The bone marrow is a vital organ uniquely suited for transplantation. Marrow for transplantation can be obtained with relative ease from a living donor in whom it is constantly being renewed. Marrow transplantation is a treatment method offering long-term survival and potential cure for patients with otherwise fatal diseases.

Bone marrow transplantation is a developing form of therapy. It is most often performed for hematological malignancies including acute myeloid leukemia, acute lymphoid leukemia, chronic myeloid leukemia, malignant myelosclerosis, pre-leukemia, lymphoma and multiple myeloma. Bone marrow transplantation is an effective form of therapy for patients with severe aplastic anemia that is non-responsive to immunosuppressive therapy. A number of congenital disorders have been successfully treated with bone marrow transplantation, including severe combined immune deficiency disease (SCID), the Wiscott-Aldrich syndrome, Fanconi's anemia, thalassemia major, sickle cell anemia, osteopetrosis and various biochemical storage diseases. These latter conditions involve mainly the pediatric age population.

There are three types of marrow transplantation. Autologous bone marrow transplantation involves the re-infusion of the recipient's own marrow cells. Usually these cells are purged of tumour cells and stored frozen. They are re-infused following a course of intensive chemotherapy and radiation designed to eradicate any residual tumour. Autologous bone marrow transplantation is an investigational form of treatment that, although promising, has yet to provide results that are superior to the best forms of conventional treatment.

In syngeneic bone marrow transplantation, the donor and recipient are identical twins.

The most frequently performed and most successful marrow transplants are allogeneic. In this situation the donor and recipient are HLA-identical, and usually are brother or sister. The role of other types of donor-recipient transplants, such as HLA-identical but not related is being investigated.

Patient selection for bone marrow transplantation depends upon a number of factors, including the disease state, age and HLA-compatibility. In general, bone marrow transplantation is restricted to patients under the age of 40 and who have a suitable donor determined by serological histocompatibility typing (HLA) and mixed leukocyte cultures (MLC). The best results have been obtained when marrow transplants have been done in patients at relatively early stages of malignant disease.

The major complications of bone marrow transplant remain graft-versus-host disease (GVHD), recurrent malignancy, and an increased susceptibility to life-threatening infection. The risks of these complications have to be weighed against the risk associated with delaying transplantation and carrying on with standard treatment regimens. It can be anticipated that if GVHD can be controlled or avoided then the number of transplants being done will increase.

A marrow transplantation program can be successfully mounted with the resources of a large medical centre capable of providing the necessary support facilities. A dedicated, highly trained medical and nursing staff and an associated research program in marrow transplantation are the essential components of the program.

GUIDELINES[4]

1. PATIENT LOAD

The number of bone marrow transplants in Canada varies from 200 to 250 per year. While the Advisory Committee on Bone Marrow Transplantation estimated the patient case load to be 214 transplants per year, indications for the procedure are expanding. By 1990 it is estimated that there will be 550 cases per year. (See Table 1, page 5.)

A minimum patient load is required to develop professional expertise for patient selection, performance of the technical procedures and the effective management of transplant related complications. A minimum of 12 transplants is required for a start-up unit. The most desirable number of transplants per center per year is 40. Additional patients would require additional nursing units.

2. INPATIENT BED REQUIREMENTS

The bed requirements for marrow transplantation are listed in the accompanying table (and Table 2, page 12). Marrow transplant recipients require single hospital rooms. Isolation facilities are necessary from the time of transplant until hematological recovery. One isolation room is required for each 10 transplants per year.

3. INPATIENT NON-BED REQUIREMENTS

A bone marrow transplant unit requires all of the services available in a large teaching hospital. (see Table 3 and 4, pages 14 and 15.) A number of specific facilities must be available in an institution developing a bone marrow transplant program:

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[4] This guideline must be read in conjunction with the section entitled "General Considerations", beginning on page 7

a) Therapeutic radiation

Therapeutic radiation facilities must be readily available to the bone marrow transplant unit. A radiation therapist should be assigned to work with the bone marrow transplant team to ensure standardization of technique and the development of the most suitable programs for pre-transplant irradiation.

Facilities for the irradiation of blood products to be administered to bone marrow transplant recipients must also be available within the Institution.

b) Pheresis Unit

A pheresis unit is required for the provision of platelet transfusions. Plasma exchanges are also frequently necessary when the donor and the recipient have a major incompatibility.

c) Intensive Care Unit

Ready access and consultation with an intensive care unit is essential because of the high incidence of respiratory problems in recipients of bone marrow transplants.

d) Dietary Services

The services of a dietitian are required as patients need special diets during the post-transplant period and advisory support in meal planning.

e) Pharmacy

Provision for providing parenteral nutrition must also be met; this is required for all marrow transplant recipients for periods ranging from three weeks to as long as six months.

f) Tissue Typing Facilities

Essential to a marrow transplant program is the ready availability of tissue typing for recipients and potential donors.

g) Cryopreservation

Centres doing autologous transplants require facilities for cryopreservation of marrow. equipment for controlled freezing, freezers for storage at -70^0C., thawing the samples and testing viability are required. For optimal storage of cell suspensions a skilled technician is necessary.

h) Blood Banking

A full service blood bank is required for a marrow transplantation program. For centres doing autologous transplants, facilities for cryopreservation of marrow are necessary.

i) Social Services

Marrow transplantation is a major undertaking for patients and their families. They are often required to travel long distances to the transplant centre, causing additional disruption to family life. The services of a social worker are required to assist in managing social and financial problems. Hostel facilities for patient and family are desirable.

j) Psycho-social Services

In addition to the support provided by medical, nursing and social services departments, more serious problems of a psycho-social nature may develop in transplant recipients or their families. The availability of a psychiatrist and psycho-social nurses for the support of these patients and their families is essential.

4. OUT-PATIENT REQUIREMENTS

Outpatient facilities are required to accommodate preoperative patients and their donors (who make on the average 3 visits in total prior to the procedure) and post-operative patients, who make 30 visits during the first year following the procedure, with lessening numbers per year thereafter. These facilities can be included as part of the inpatient facilities or as a designated area in the outpatient or day care services of the institution. Consideration must be giving to the fact that these patients often are seen on short notice and out of regular working hours. Donor workup is done in the outpatient area.

5. PROGRAM ALLOCATION

Transplant centres should be located in large medical centres capable of providing the necessary supportive care and allowing ready access for patients. Such units can most readily be established in teaching hospitals with an in-house medical staff. Based on the above-noted requirement, up to 11 appropriately staffed and equipped units would meet the marrow transplant needs for Canada.

6. PROGRAM RELATIONSHIPS

Marrow transplant requires a specific designation of personnel and resources. Close collaboration is required for surgery, therapeutic radiation and various medical subspecialties. A marrow transplant program has a wide impact on hospital resources ranging from nursing, food services, social services, central sterile supply, pharmacy, blood bank and other essential hospital services. Usually, a marrow transplant program is part of, or associated with, a program for treatment of, leukemia and other hematological malignancies.

It is desirable, although not essential, that a marrow transplant program utilize services required for other transplant programs and end-stage disease programs. For example, tissue typing services, the

determination of drug levels such as cyclosporine and parenteral nutrition services could be shared.

7. ORGANIZATION AND POLICIES

7.1 Medical Direction

A Unit Director should be appointed, who, in association with other staff, would be responsible for the development of a bone marrow transplant program, its operation, integration and coordination within the institution. The Unit Director responsible for the transplant program should report to the appropriate governing body of the institution, with his/her appointment subject to the same review procedures as for other program directors.

7.2 Policies

Policies and procedures should be established to ensure standards at least comparable with those of other major bone marrow transplant centres. Special policies and research protocols would be reviewed with appropriate internal and/or external review boards, e.g. the institutional clinical trials committees or affiliated university human experimentation committees. In keeping with institution's policy, regular reviews of specific aspects of the program and audits to ensure quality of patient care must be undertaken. (See also page 17 and Annexe C, page 105).

8. PERSONNEL REQUIREMENTS

8.1 Medical Staff

Unit Director: The director of the transplant unit will be a physician devoting 100 per cent of his time to the program and closely related activities. He/she will have specific training and experience in marrow transplantation. His/her specific duties will include:

i) Organization and supervision of the marrow transplant centre.

ii) Development of programs including the stimulation and coordination of transplant related research.

iii) Oversight of audit, quality assurance and evaluation routines.

iv) The development of training programs for physicians, scientists and other staff in cooperation with existing programs within the institution.

8.2 Other Medical Staff

Additional medical staff will devote up to 50 per cent their time to transplant patient care. Ordinarily physicians in these positions will have varied backgrounds including hematology, immunology, oncology, and transplantation. Assuming a 50 per cent time allocation, one such physician per 10 transplants per year may be required.

8.3 Consulting Physicians

An institution undertaking the establishment and operation of a marrow transplant unit will require the following consultants and facilities related to the specialties: respirologists, infectious disease consultants, dermatologists, gastroenterologists, surgeons, cardiologists, and therapeutic radiologists.

8.4 Nursing Requirements

Nursing requirements for a marrow transplant unit necessitate staffing and training equivalent to an intensive care unit. The nurse/patient ratio should be determined using suitable staffing standards related to patient classification systems. Isolation procedures are a routine part of marrow transplant nursing. Special training is needed for nurses to cope with the psychosocial problems of patients and their families during the post-transplant period.

Transplant patient coordinators, usually nurses, have been effective in coordinating patient related activities in kidney and other organ transplant

centres. The role of such individuals in the bone marrow transplant centre is less well established. Financial support must be provided for a coordinator by any centre contemplating establishing a bone marrow transplant program.

The staff education unit of the supporting institution must be prepared to provide specialized teaching and training related to nursing in a marrow transplant unit.

8.5 Staff Training and Qualifications

For the establishment of a bone marrow transplant unit specially trained medical and nursing staff is required. Formal training programs do not exist for physicians, but any one assuming direction of a unit must have experience in an existing unit in Canada or elsewhere. Similar experience is desirable for key nursing staff.

9. EQUIPMENT

The equipment required for a bone marrow transplantation unit is available in most tertiary referral centres. Specific requirements include the following items:

1. A blood cell separator capable or both platelet pheresis and plasma exchange

2. Radiation equipment suitable for the irradiation of blood products.

3. Equipment for cryopreservation of marrow cells in a form suitable for re-infusion.

10. SPACE ALLOCATION AND SPECIAL DESIGN FEATURES

Marrow transplant units should be developed as a self-contained entity. For a unit undertaking 40 to 50 transplants per year, five isolation rooms with controlled flow of filtered air and with individual bathrooms are required. These rooms are used for

patients immediately post-transplant. For patients at other stages of the pre and post-transplant process, such a unit will require single bedrooms with individual baths and showers. Provision for the following facilities are needed within the transplant unit:

1. A patient dining area and lounge.

2. Nursing station including space for drug storage and preparation, dictation, computer facilities and clerical activities.

3. A food preparation area.

4. Examination/interview room.

5. Conference room.

6. House physicians' room.

7. Unit Director's office.

8. Head Nurse/Transplant Patient Coordinator's office and staff lounge.

11. PEDIATRIC CONSIDERATIONS

About one-third of bone marrow transplant recipients are patients in the pediatric age group. Institutions undertaking marrow transplantation for recipients of this age must have general medical and surgical services capable of providing all facets of care. The indications for marrow transplantation in children include hematological malignancies, severe aplastic anemia and congenital disorders. The survival rates for allogeneic marrow transplant recipients with hematological malignancies and with aplastic anemia are better in the pediatric age group due to a decreased incidence of graft-versus-host disease. The congenital immune deficiency syndromes present a special category of disorders often requiring increased supportive care in terms of isolation facilities, both before and after marrow transplantation.

12. INFORMATION CONSIDERATIONS

Although no national register of bone marrow transplants exists, it is desirable that such a system be established. Marrow transplantation is a developing area of medical practice. Essential to the functioning of a unit where research and good patient care are closely interrelated, are facilities for accurate data collection and analysis. Such data collection should be computer-based and shared with sister institutions and with a national data bank when such is established, to ensure the optimum standards of care and research and to facilitate the exchange of information relevant to transplantation.

HEART AND HEART/LUNG TRANSPLANTATION[5]

PREAMBLE

Heart and heart/lund transplantation are currently indicated for patients with advanced forms of heart and/or lung disease, in whom no realistic hope for extension of life or palliation exists with ordinary forms of medical or surgical intervention.

For centers already performing kidney, liver or other organ transplantation, the effect of a clinical program in heart and heart/lung transplantation is likely to increase organ donation.

The regional center should provide the care necessary for managing patients pre-operatively, peri-operatively and for long-term management, should test and evaluate new therapeutic strategies as they become available, and should promote inter-center collaboration so that advances may be made as rapidly as possible. The referring center may also be able to contribute to long-term care as local expertise is developed.

There is much to be gained by association with other centres. In a given area this might include other liver and kidney transplantation programs. By association, new knowledge is gained in patient management and optimal use is made of multi-organ donors. To this latter point, for example, sharing of organ donation services, including air ambulance, may be possible.

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5 This section should be read in conjunction with the Guideline on Cardiovascular Services in Hospitals, published by the Department of National Health and Welfare, Health Services and Promotion Branch, Ottawa, 1986

GUIDELINES[6]

1. PATIENT LOAD

End-stage cardiac disease represents the most common cause of death in North America. The two most common conditions amenable to transplantation are cardiomyopathy and ischemic heart disease. In Canada, approximately 1500 individuals between the ages of 10 to 55 years could benefit from cardiac transplantation. Possibly a similar number of individuals with primary pulmonary hypertension, Eisenmenger's syndrome or primary lung parenchymal disorders could benefit from heart/lung transplantation.

Two additional factors, temporary mechanical circulatory support and extension of the recipient candidate age limits could dramatically increase the number of patients that could benefit from transplantation. Successful transplantation of individuals younger than 10 years of age and greater than 55 years of age indicates the potential for increasing the number of potential recipient candidates dramatically, i.e. two-to-four fold.

Donors currently need to be under 40 years of age and be otherwise healthy. This reduces the supply considerably. Calculations based on the data contained in the 1983 Report of the Canadian Renal Failure Register indicate that over 700 hearts could be available in 1990. However it is unlikely that the need for heart/lung transplantation will ever be met since only one heart/lung donor occurs for every four to five heart donors.

The Working Group on Vital Organ Transplant Centers recently recommended the more conservative

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[6] This guideline must be read in conjunction with the section entitled "General Considerations", beginning on page 7.

planning figure of 500 heart and 50 - 100 heart/lung transplants annually. (See Table 1, page 5.)

The proportion of potential heart of heart/lung transplant candidates being managed medically or surgically at the transplant institution varies by geographic region, from 10 to 100 per cent. This fact has important implications in terms of both the utilization of existing services outside transplant centers, and the potential impact of a new, full program in heart and heart/lung transplantation.

Number of Patients Admitted for Work-up

Each center may expect to have approximately 150 - 200 cardiac and an equal number of heart/lung transplant candidates assessed annually for transplantation. The distribution of the burden of this activity will depend on the proportion of such patients that are assessed outside the transplant center, and the quality and thoroughness of the assessment.

Up to 50 heart and 10 heart/lung transplantation procedures per cent would be performed annually, depending on institutional resources and donor availability.

Follow-up Care

Givin current survival statistics for cardiac transplantation, of 90 to 95 per cent and 65 to 70 per cent at one and five years respectively, the number of patients requiring follow-up care by the end of the fifth year would be around 216. For heart/lung transplants the corresponding figure could be around 40.

2. INPATIENT BED REQUIREMENTS

Tables 2 and 5, on pages 8 and 49, summarize the bed requirements for this service. These provisions include the following requirements:

Cardiology

a. An average per patient of three days to fully evaluate patients for transplantation.

b. Full support for 45 days in hospital for 30 patients prior to either death or transplantation.

c. 14 days of re-hospitalization in the first year following transplantation for 10 per cent of successfully transplanted patients, and for five per cent per year thereafter. In subsequent years, a smaller number of patients will require re-hospitalization, but there is no data on this requirement.

d. Three days annually per survivor for cardiac biopsies and catheterization studies.

Cardiothoracic Surgery

a. One day prior to surgery for 45 patients, in addition to those already present on cardiology.

b. Intensive Care Unit (ICU) and ward stay will depend upon which type of procedure is performed, the complications associated with the procedures and whether or not there is a "step down unit" available for these patients. In the discussion below, the figures in parentheses indicate the numbers of days patients could spend in a step down unit that otherwise would be spent in the ICU:

i) 10 (6) ICU days and 25 ward days for cardiac transplant patients without complications (25 per cent).

ii) 15 (3) ICU days and 20 ward days for patients with mild to moderate complications (62 per cent).

iii) 35 (10) ICU days and 40 ward days for cardiac transplant patients with severe complications (12 per cent).

iv) 35 (15) ICU days and 40 ward days for heart/lung transplantation recipients.

For 50 heart and 10 heart/lung transplants annually, five reverse isolation type Intensive Care Unit rooms would be required in addition to seven beds on the ward. Of the ward beds, two should have reverse isolation capabilities and the remaining five may be private rooms.

3. INPATIENT NON-BED REQUIREMENTS (SUPPORT SERVICES)

The departments and support services essential or desirable for heart and heart/lung transplantation have been outlined in Tables 3 and 4, on pages 14 and 15.

It is anticipated that each transplant patient will require an additional 11 800 work units in laboratory medicine and 11 700 Federal-Provincial work units in the microbiology and virology laboratories. Therefore 1.4 million Federal-Provincial work units would be generated for 60 patients.

The organ donation team consists of a cardiac surgeon or fellow with expertise in the removal of a heart or heart and lungs together, a first assistant, and experienced scrub nurse and a transplant patient coordinator.

4. OUT-PATIENT REQUIREMENTS

Out-patient facilities are required for follow-up: surveillance for rejection, infection, malignancy, hypertension and medication control and in the case of heart/lung transplant recipients, pulmonary function testing and out-patient physiotherapy. Cardiac catheterization services are also required to perform endocardial biopsies.

5. PROGRAM ALLOCATION

The development of a heart transplantation facility, with or without heart/lung transplantation capability, is best centered where full laboratory backup and related services exist, such as those required for kidney transplantation programs. Ideally, heart and heart/lung transplantation will be one component of a multi-organ transplantation program. Such centers would be geographically distributed throughout Canada. Programs for heart and heart/lung transplantation should be established only at centers with active cardiology, chest medicine, and cardiovascular and thoracic surgical programs already in existence, which also have 24 hour in-house dedicated medical support for transplant candidates and recipients. Ideally, such centers would already have established kidney transplant programs, so that full support services already in existence can be easily tapped by the new transplantation program.

Based on the estimates outlined above, one center for each 2.5-3.0 million population could perform approximately 50 heart and up to 10 heart/lung transplants yearly by 1990 (a total of 10 centers for Canada). A goal of 50 or more transplants per center is desirable to produce optimal efficiency and cost effectiveness with the best possible clinical results.

6. PROGRAM RELATIONSHIPS

Within the Region

Because of the short cold-ischemic time for the heart (five hours) and lungs (one hour), both heart and heart/lung transplantation procedures must be considered emergent. From the time that the heart is removed from the donor, it should be implanted and perfused within four to five hours. For heart/lung transplantation, as there is no effective and reliable method for preserving the lung, donors must be transported to the recipient center. Therefore, ground and air ambulance services are essential for

the successful operation of a heart and heart/lung transplantation program.

The general requirements for a successful program in heart and heart/lung transplantation include affiliation with an active kidney transplantation program and, ideally, with other solid organ transplantation programs, for the efficient use of support services.

Within the Center or Program

The performance of 50 to 60 transplants per year affects all areas of the hospital, and requires a commitment to heart and heart/lung transplantation of a truly dedicated nature. Accommodation must be made for such patients in the Intensive Care Unit, on the wards and in the operating rooms, so as not to adversely affect the provision of care to other patients. Additional cardiac catheterization may require added staff resources.

With Other End-Stage Treatment Modalities for Heart Failure

For moderate-term support, temporary circulatory support in the form of ventricular assist devices and artificial hearts are currently able to provide circulatory support prior to transplantation.

7. ORGANIZATION AND POLICIES

7.1 Program Organization

A program director should be appointed, to be responsible for the organization of the program, assignment and monitoring of all clinical responsibilities, the coordination and performance of all transplantation procedures and the integration and evaluation of new or experimental protocols into the clinical setting and long range planning. In addition to these major clinical responsibilities, the director will serve as a catalyst for research and educational activities surrounding the transplant program.

7.2 Patient Management Protocols

Protocols for the management of donors and recipients must be agreed upon and patients identified early in the course of their disease. These include protocols established with other medical facilities in the catchment region of the transplant program, to make heart or heart/lung transplantation fully available to patients unable to obtain additional benefit with conventional therapies.

7.3 Policies

Special policies must be developed for pre-operative assessment and operative activities for both recipients and donors, and for post-operative management strategies for recipients. (see Section 8.2, General Considerations, page 17, and Annex C, page 105).

8. PERSONNEL REQUIREMENTS

8.1 Program Director

The program director may be a transplant surgeon, cardiologist immunologist or other appropriately qualified specialist. The individual chosen should have knowledge and/or experience in all facets of the program, along with administrative or organizational abilities.

8.2 Other Medical Staff

Cardiologist: At least two cardiologists are required for a transplantation program of 50 heart and 10 heart/lung transplantation patients per year. They must have knowledge and/or experience in patient selection and management for transplantation, endocardial biopsies, cardiac catheterization, monitoring of rejection and infection in the immunosuppressed patient, and use of immunosuppressive drugs.

Chest physician: At least one chest physician should be involved with the selection and pre- and

post-operative lung assessment of heart/lung transplant patients.

Transplant Surgeon: The transplant surgeon must have training and experience in routine cardiovascular and thoracic surgery with specialized training in heart and heart/lung transplantation, including all related surgical procedures, endocardial biopsies, the use of immunosuppressive drugs and the management of the immunocompromised patient following extensive surgery.

Anesthetists: Anesthetists assigned to heart and heart/lung transplantation must have extensive experience with routine cardiac surgery and be knowledgeable concerning the unique pathophysiological status of the heart and heart/lung transplant recipient (denervated heart and lungs, frequent liver dysfunction and associated coagulopathy, sterile technique and response to inotropic, vasoactive and antiarrhythmic agents).

Pathologists: At least two pathologists with an interest in transplantation and knowledge or experience in the pathology of heart and lung rejection are required. They should provide 24 hour coverage for the emergency assessment of tissues submited for evaluation of rejection or infection.

8.3 Nursing Staff

As noted in the section on general considerations common to all units, in all phases of transplantation, nursing staff must be knowledgeable in the management of individuals with compromised cardiopulmonary function. Following the transplantation, nurses must be able to provide care to the immunosuppressed patient, and be skilled in identifying the signs and symptoms (short of cardiac biopsies) of rejection. The nurse and/or transplant patient coordinator assisting in the follow-up when the patient is discharged must have a knowledge base comparable to that of the ward nurse.

As the care generated by the transplant program is complex, it is important that staff education proceed in a planned, formalized fashion. The limited number of post-graduate cardiovascular programs in Canada is unable to supply sufficient specially educated and highly skilled nurses to care for heart and heart/lung transplant patients. The education of staff nurses and other staff must have the same degree of emphasis as the other program components. Such functions may be performed by a clinical nurse specialist or a unit-based instructor.

8.4 Other Staff

Social Services: The role of the social worker is the assessment, support and follow-up for the patient and family, as well as the coordination of emotional, financial and housing assistance as required pre- and post-operatively.

The physiotherapist involved with the heart and heart/lung transplantation program must be an individual who is not only capable of conducting all pulmonary physiotherapy and physical rehabilitation therapy following transplantation, but must also be an individual who has specialized knowledge in the unique function of the denervated heart and lungs.

9. EQUIPMENT

Little unique equipment is required to perform heart or heart/lung transplantation, except the cardiac bioptomes and transport equipment. Other added equipment may be necessary to accomodate increases in workload.

10. SPACE ALLOCATION AND SPECIAL DESIGN FEATURES

There is no unique space requirement for this service, but additional spaces of various types may be needed.

11. PAEDIATRIC CONSIDERATIONS

Although infants and children less than 10 years of age have undergone successful heart or heart/lung transplantation, the number of such patients who have benefitted and who are likely to benefit in the near future is small. With current technology for monitoring rejection and the scarcity of paediatric donors, fewer than five per cent of an active transplant centre's caseload will consist of children.

Because of the special requirements for heart and heart/lung transplantation, in terms of donor and recipient selection and management and of surgical and post-operative skills that only develop with a sufficient number of transplantation procedures, it is highly desirable to accommodate the special needs of the paediatric recipient as a part of an adult transplantation program. (See page 21).

TABLE 5

BED REQUIREMENTS

(For 50 Heart and 10 Heart/Lung Transplants per Year)

CARDIOLOGY

	Assessment+	Support+ prior to transplantation	Admission for medical support	Annual studies	Total
75% Occupancy	4.4	4.9	0.3 (0.8)*	0.5 (2.3)*	10.1 (12.0)*
Recommended	5	5	0 (1)*	0 (2)*	10 (12)*

\+ If 50% of the heart/lung transplant candidates are assessed and supported while on the pulmonary service, then 2.0 less beds would be required for cardiology, but 2.0 more beds would be required for pulmonary medicine.

Over the course of five years, additional bed support will be required and for annual studies.

CARDIOVASCULAR AND THORACIC SURGERY

	Pre-operative beds	Post-operative beds	ICU
75% Occupancy	0.2	5.8	4.2
Recommended	1 *	6	5

* It would be preferable that this need be fulfilled by a cardiology assessment or other bed.

LUNG TRANSPLANTATION

PREAMBLE

Lung transplantation, the newest of the successful organ transplants, is now being performed as an experimental procedure with excellent early results, suggesting that this will become a therapeutic procedure. The previous problem limiting the application of lung transplantation - the bronchial anastomosis - now appears to have been solved. The procedure is available for patients who are in end-stage respiratory failure due to non-infectious destructive pulmonary disease in which severe heart disease or pulmonary hypertension has not developed. The most common diagnosis will be progressive idiopathic pulmonary fibrosis. The number of suitable candidates in the country cannot be estimated at present. However, it appears that the number of donors with suitable lung dimensions and quality is small, and that this will be the rate-limiting step in application of lung transplantation.

GUIDELINES[7]

1. PATIENT LOAD

This cannot be estimated until results with various lung diagnoses can be assessed. As of 1986 only one centre exists in Canada. However, it would be reasonable for a centre developing heart/lung transplants for primary pulmonary disease to consider the possibility of single lung transplants.

2. INPATIENT BED REQUIREMENTS

Estimates indicate that four patients will be admitted for assessment for each patient transplanted, and that each assessment will require about 10 days in hospital, for studies such as pulmonary function and cardiac evaluation. Many of these patients will require a rehabilitation program to restore strength before the procedure, in order to improve their course in the post-operative period. Patients are initially nursed post-operatively in an intensive care unit.

3. INPATIENT NON-BED REQUIREMENTS

A pulmonary function laboratory and facilities for membrane oxygenation in the post-operative period will be two features that will be necessary to add lung transplantation. (See Tables 3 and 4, Pages 14 and 15.)

4. OUT-PATIENT REQUIREMENTS

These patients can be followed in the existing rural or multi-organ transplant follow-up system.

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[7] This guideline must be read in conjunction with the section entitled "General Considerations", beginning on page 7

5. PROGRAM ALLOCATION

This cannot be estimated until the current experience is extended.

6. PROGRAM RELATIONSHIPS

This will be similar to the heart, heart/lung or kidney transplant programs.

7. ORGANIZATION AND POLICIES

This should be similar to those of the heart or heart/lung transplant programs.

8. STAFFING CONSIDERATIONS

The principal requirement distinguishing lung from other programs is intensive involvement of thoracic surgeons and chest physicians. A committed anaesthetist is also necessary. Aside from those persons, the other personnel requirements are similar to those of the heart, heart/lung and kidney programs.

9. EQUIPMENT

The special equipment required is a membrane oxygenation apparatus for support if necessary during the post-operative period. Otherwise the usual equipment of a thoracic surgery and pulmonary medicine division, coupled with another organ transplant program (i.e. kidney) will suffice.

10. SPACE ALLOCATION AND SPECIAL DESIGN CONSIDERATIONS

There are no special considerations for this service.

11. PAEDIATRIC CONSIDERATIONS

At the moment, no indications exist for the procedure in young children.

LIVER TRANSPLANTATION

PREAMBLE

Results obtained during the last five years demonstrate that liver transplantation offers a definitive treatment which may prolong life in patients suffering from end stage liver disease. Approximately 70 per cent of current liver recipients are alive one year following surgery. Improvement in survival is related to the introduction of cyclosporine. The use of a veno-venous by-pass without systemic anticoagulation has proved to be a major technical advance in the performance of this demanding operation.

Matching: ABO blood group matching and a negative leukocyte crossmatch are desirable. However in the few cases where blood group barriers have been breached, or where the leukocyte crossmatch was positive, there was no apparent hyperacute rejection. Therefore, in desperate need, violation of blood group matching or leukocyte crossmatching would appear acceptable. The poor correlation between HLA matching and clinical outcome has led most groups to ignore HLA matching as a selection criterion for liver transplantation. Matching or body build and weight are essential and has resulted in a tragic shortage of livers in the pediatric age group.

Any acceptable kidney donor age 50 or less is a potential candidate for liver donation. Additional specific requirements include normal laboratory values of liver functions, particularly when abdominal trauma is suspected, absence of history of previous hepatic disease and normal cardiac function.

The standard technique of transplantation of the liver involves the removal of the diseased organ and its replacement in anatomical position by the graft. An alternative method, the auxiliary liver transplantation, where an extra liver is inserted at an ectopic site, would appear to be a much simpler procedure and offer major advantages, since the sacrifice of the remaining function of the original liver is

avoided. However that operation has been plagued by technical problems and has never gained acceptance.

In many forms of liver disease, the precise indications and timing of liver transplantation remain uncertain and controversial. Further research is obviously needed to answer these questions.

GUIDELINES[8]

1. PATIENT LOAD

The estimated number of transplants per year needed in Canada is 200, based on an epidemiological study done by the Canadian Liver Foundation and presented at a special workshop in 1984. This study revealed that of 2,770 patients who died annually of liver diseases between 1979 and 1982, 186 a year might have been suitable candidates for a transplant. These numbers correlate very well with projections from the United States, based on similar studies where a rate of eight transplants per million population has been calculated. The Canadian Working Group on Vital Organ Transplant Centers estimated in July 1985 that 223 cases a year would need liver transplants for the next five years. (See Table 1 on page 5.)

2. INPATIENT BED REQUIREMENTS

Current experience shows an average length of stay of 60 days for adults. Given 25 patients a year, seven beds will be required. In addition, at least two or three ICU beds should be available for post-operative care and for patients in terminal liver failure awaiting a transplant. The usual period of intensive care stay after a liver transplant is 14 days, assuming that a step-down unit is not available. (See Table 2 on page 12.)

3. INPATIENT NON-BED REQUIREMENTS

These specific supporting departments and services listed in Table 3 on page are considered essential or highly desirable.

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[8] This guideline must be read in conjunction with the section entitled "General Considerations", beginning on page 7.

A successful liver transplant program will result in an increased workload on supporting services. Those most likely to be affected are anesthesia, the operating room, the intensive care unit, the blood bank and hemodialysis. Radiology, microbiology, hematology and biochemistry will be required to regularly perform sophisticated tests on an emergency basis.

Organ retrieval services: An expert retrieval team, mobile and on call 24 hours a day is required. Access to ground-air transportation facilities in an essential and often underestimated requirement of a successful program.

The operation itself will last between twelve to twenty hours and require from 20 to sometimes as much as 100 units of blood. Added personnel will be required in the blood bank, biochemistry, coagulation lab and operating room when a liver transplant is performed.

If such an operation is done during week days, there will be a disruption of the regular operating room schedule. If it is repeated twice in the same week, the blood bank will be depleted, the regular working schedule of the operating room will be affected and the personel involved will be exhausted and unavailable for their normal working shifts.

Surgeons, anesthesiologists, hematologists, nurses, transplant patient coordinator(s), pharmacists, and technicians from biochemistry, hematology and blood bank will have to be on call permanently.

4. OUT-PATIENT REQUIREMENTS

Out-patient facilities are essential for follow-up. After leaving the hospital, transplant patients are seen twice weekly for a couple of months for clinical and extensive laboratory evaluation to monitor liver functions and cyclosporine levels. Liver biopsies will be performed on demand depending on clinical status.

Following the initial two month period, transplant patients will be seen in the outpatient clinic once a week for the next two months, and twice monthly for the rest of the first year. After the first year, follow-up visits will be at three month intervals.

As the number of transplanted patients increases, given the current success rate of 70 per cent at one year, the workload in the outpatient clinic will necessarily go up, even if it remains constant in the ward. In a program performing 25 transplants a year, after five years there would be around 80 patients to be followed. Provisions for space, personnel and lab work should be made accordingly.

5. PROGRAM ALLOCATION

Liver transplantation should be carried out only in institutions offering the full array of services required of a tertiary care facility, where critical care capabilities are at the highest level and medical staff coverage is available in house 24 hours a day. Ongoing research programs in liver deseases, and willingness to prospectively collect and share data in a coordinated, systematic and comprehensive manner are desirable.

These prerequisites should limit the location of liver transplant centers to teaching hospitals where hepatic surgery is already carried out and with programs in graduate and post-graduate medical education.

A minimum of 12 procedures per year is recommended to maintain surgical and other skills. While the optimum number is estimated to be about 25 cases per year, the upper limits will depend on the size of the institution and its willingness to tolerate this. One center is recommended per three million population.

6. PROGRAM RELATIONSHIPS

Affiliation to a regional organ procurement organization with access to national and continental network

of donor identification is essential. Association with other centers in Canada performing liver transplants is mandatory so that data might be shared and optimal results obtained. This need is magnified by the short cold ischemic storage time for livers.

A liver transplant program should be integrated into a multi-organ transplant program, coordinated under a program director. Such a multi-organ program will normally be put together inside the framework of a university.

7. ORGANIZATION AND POLICIES

A liver transplant program will be run by a unit director selected from among the specialists forming the core of the program (surgeon, hepatologist, anesthetist). Because of the complex nature of the process, the program director must deal with all departments and services listed in Table 3, and be accountable to heads of these departaments for use of their personnel and equipment. The job will be mainly one of coordination. In addition to the above, the director will:

i) be responsible to set up committees to overview patient selection from medical and ethical standpoints and quality of care,

ii) organize regular scientific sessions for members of the team where current knowledge will be presented and updated,

iii) ensure that research programs are being conducted and properly funded,

iv) report regularly to designed executive authorities reviewing quality of care,

v) be in close contact with head administrators since the requirements for conducting a liver transplant program by an institution are formidable, and

vi) coordinate relations with other services inside the institution and ensure regular contacts with other transplant programs outside the institution.

Special policies must be developed for pre-operative assessment and operative activities for both recipients and donors, and for post-operative management strategies for recipients. (See Section 8.2, General Considerations, page 7, and Annex C, page 105.)

8. PERSONNEL REQUIREMENTS

8.1 Medical Personnel

The team consists of specialists directly involved in the day-to-day care of these patients and the performance of the operation; these include surgeons, hepatologists and anesthetists. Also, experts in infectious diseases, nephrology, chest medicine, pathology, haematology and immunology must be available at all times. Emotional evaluation and support of patient and family may require psychiatric service involvement.

Two surgeons experienced in liver surgery and trained in transplantation are needed to perform the operation. Cold ischemic time is limited to eight hours; organ retrieval in the donor and total hepatectomy in the recipient must overlap. Post-operative care is intensive and between 25 and 50 percent of patients will have to be reoperated upon for various complications. A program performing around 25 liver transplantations a year or more will need surgeons and 3 anesthetists well trained in the field.

Additional surgeons will be needed to assist the transplant surgeons in the operating theater. These assistants can be residents in surgery or general surgeons with no special expertise in transplantation. The responsible surgeons must possess skills in microsurgical techniques.

8.2 Nursing Personnel

In all phases of liver transplantation nursing staff must be knowledgeable in the care of individuals with compromised hepatic function.

To launch a new program, experience in an established transplant centre is recommended for both the operating room staff and for the intensive care unit staff.

8.3 Other Staff

Social service availability is essential to assist patients and families to cope with financial and social difficulties that will occur before, during and after transplantation. An essential role of the social service is to assist with housing for patients and members of their family while awaiting transplantation.

A perfusionist with training acquired in cardiac surgery will be need when liver transplantation in adults requires the use of veno-venous by-pass involving pump driven extra-corporeal circulation.

8.4 Staff Training and Qualifications

See General Considerations section 9.4, on page 21.

9. EQUIPMENT

The specific equipment needed or useful for a liver transplantation is listed below:

- a pump driven veno-venous by-pass
- a rapid infusion pump
- a blood saver auto-transfuser
- a thrombo-elastogram

10. SPACE ALLOCATION AND SPECIAL DESIGN FEATURES

Although liver transplantation can be done without isolation facilities, it appears desirable to house

these patients in a special unit composed of private rooms.

11. PEDIATRIC CONSIDERATIONS

Children (under 18) have accounted for 1/3 to 1/2 of liver recipients. Since the introduction of cyclosporine, results in children have been better than in adults, with a 10 to 20 per cent advantage in survival at one year. Because match of body frame and weight is essential, it is more difficult to find organs for children: the smaller the patient, the more difficult to find a suitable donor. Consequently, a pediatric program must have access to transportation facilities if it is to be successful. Children now make up about 10 per cent of liver recipients.

Whenever possible, to meet the special care requirements of children, the operation should be conducted in a pediatric hospital. However, the high volume of cases necessary to attain and maintain surgical and post-operative management skills is more likely to occur in adult centers. Accordingly, it may be desirable to set up transplant teams that will work in both adult and pediatric institutions.

PANCREAS TRANSPLANTATION

PREAMBLE

The majority of pancreas recipients have been patients in end-stage diabetic kidney failure who have received a current kidney transplant. Therefore, this program for the present should be considered as an adjunct to a kidney transplant program, with all other indications considered experimental in nature.

Patient survival has improved so that for 1984 cases it was 75 per cent at 12 months. Because of the differences in case selection from centre to centre it is difficult to compare survival in diabetic kidney transplant recipients who receive a pancreas with those who do not. There have been no randomized controlled studies. It is clear that in recipients not in end-stage kidney failure who receive a pancreas only, graft survival is superior in recipients of both a kidney and a pancreas (33 per cent vs. 25 per cent).

Despite improvements, pancreas transplants do not do as well as other organs. One year graft survival is only 40 per cent compare to 70-90 per cent for kidney, heart and liver despite identical immunosuppressive drugs. Only 15 per cent of grafts are functioning past four years.

Although the evidence is not entirely clear, it is likely that the excessive loss in this organ compared to others is technical rather than representing a difference in immunological sensitivity. The factors that have been identified include preservation damage, duct obstruction leading to fibrosis and vascular thrombosis.

As a consequence of these limitations the procedure tends to be restricted to these patients in whom the immediate or short term consequences of their present diabetic condition are likely to be more risky than the risks associated with end-stage diabetic nephropathy who have undergone kidney transplan-

tation and must receive immunosuppressive drugs anyway.

For those patients who have a technically successful graft, there is now evidence for an improvement in and arresting of diabetic complications including retinitis, neuropathy and atherosclerotic vascular disease. Therefore, for the above-noted indications the procedure may be considered therapeutic.

GUIDELINES[9]

1. PATIENT LOAD

The current rate of entry of new patients to dialysis is 58 per million, of whom 20 percent (10 to 30 percent various regions) are diabetic. If 66 per cent these 217 patients are suitable pancreas transplant candidates, then the projected rate for Canada would be five per million per year, or 125 per year for referral for the procedure, i.e. for diabetic patients in kidney failure only.

2. INPATIENT BED REQUIREMENTS

At least one bed for every 10 transplants per year is required but it is assumed that the majority of these patients will have concurrent kidney grafts and therefore beds over and above the complement assigned to the kidney program are unnecessary (see kidney section). This would change if or when indications broaden to include diabetics not in kidney failure. Complications will be higher in this group, and depending on the number of pancreas grafts, extra beds may be required. (See Table 2, page 12.)

3. INPATIENT NON-BED REQUIREMENTS

These will be identical to those of the associated kidney program. (See Tables 3 and 4, pages 14 and 15.)

4. OUT-PATIENT REQUIREMENTS

Diabetic day care facilities are a necessity and must include the ability to conduct specialized tests of pancreatic function. (See guidelines for Diabetic Day Care Centre). Since most if not all of these

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[9] This guideline must be read in conjunction with the section entitled "General Considerations", beginning on page 7.

patients will have had a kidney transplant, appropriate follow up will be as for kidney transplant patients.

5. PROGRAM ALLOCATION

The results reported to the Transplant Registry indicate strongly that success comes with experience. A rate of 12 per year or one per month would likely be an adequate minimum.

Because of the intimate relationship with kidney transplantation, only those programs with at least 18 diabetic patients referred for dialysis or about 60 to 180 (depending on the region) total new referrals for dialysis per year will produce one pancreas graft per mont. A maximum of six regional pancreas transplant centres is therefore required (to 1990).

6. PROGRAM RELATIONSHIPS

In addition to the close dependence on the kidney failure program and its relationships, pancreas transplantation requires specific collaboration with diabetology and its associated programs. (Diabetic day care, dietetic counselling, social services, rehabilitation and orthotic services, and laboratory services equipped to do such tests as serum insulin and glucagon levels, endocrine stimulation tests, glycocylated hemoglobins.)

7. ORGANIZATION AND POLICIES

A pancreas transplant program must be integrated into a multi-organ transplant program. Because pancreas and liver share a common blood supply, procedures and priorities must be in place to ensure appropriate allocation of donor organs. Since the majority of pancreas recipients will also be kidney recipients, selection criteria, preoperative assessment protocols and postoperative care manuals integrating kidney and pancreas considerations must be prepared. Provisions for auditing outcome including morbidity and mortality results must be in place. (See also corresponding section under kidney Transplantation Guidelines.)

8. PERSONNEL REQUIREMENTS

8.1 Program Director

This person would be a physician trained in transplantation and knowledgeable in either diabetes, pancreas surgery or both, who would report to the Director of the Multiorgan Transplant Program. The duties would include:

- overall direction of the pancreas transplantation inpatient and outpatient services
- preparation and supervision of clinical protocols.
- coordination of training and research in the discipline.
- organization of the pancreas retrieval and implementation teams.

8.2 Other Medical Staff

Closely Associated Medical Staff: These include a transplantation nephrologist, a diabetologist, an immunologist and transplant surgeons.

Consulting Physicians: These include infectious disease consultants, a vascular surgeon, a neurologist, an ophthalmologist and a physiatrist.

8.3 Nursing Staff

These are included in the complement for the kidney transplant unit.

8.4 Other Staff

As outlined in the section on kidney transplantation.

9. EQUIPMENT

None other than that required for kidney transplantation and pancreas surgery.

10. SPACE ALLOCATION AND SPECIAL DESIGN FEATURES

These are identical to those for kidney transplantation.

GLOSSARY

ALG: see anti-lymphocyte globulin

allo a prefix describing genetic non-identify of two members of the same species; hence:

alloantibody: antibody which reacts with an alloantigen

alloantigen: a structure which differs between two members of the same species i.e. HLA antigens

antibody: an immunoglobulin protein capable of binding to another substance (e.g. a protein) in a specific manner.

anti-limphocyte globulin (ALG): antibodies produced in another species (often horse) against human lymphocytes. Strongly immuno-suppressive. Always given intravenously.

antigen: a structure which can specifically bind to an antibody.

auto a prefix describing the relationship of one's tissues to oneself

Brain Death death of the brain stem and the higher centres.

B cells: lymphocytes which originate in bone marrow and make antibody.

Complement: a set of proteins found in serum which lyse antibody-coated cells.

cross-matching: testing the serum of one person (the recipient) for antibody against the cells of another person (the donor).

cyclosporine: an antibiotic-like substance derived from a fungus, capable of producing potent suppression of the immune response. Usually given by mouth.

cytomegalovirus (CMV): a common virus which can cause severe illness in immunosuppressed persons.

emotionally-related: a term used to designate a potential living kidney donor who is genetically unrelated to a potential recipient, but related by emotional bonds (e.g. a spouse, a close friend).

first degree relatives: parents, children or siblings.

Graft-versus-Host Disease a multi-system syndrome occurring after allogeneic bone marrow transplant, characterized by skin rashes, GI dysfunction and liver dysfunction. It may be either acute or chronic in nature.

histocompatibility: the degree of similarity (compatibility) between the tissues of two individuals.

haplotype: the set of genes in one area of a particular chromosone i.e. HLA haplotype is the set of HLA antigens encoded by a particular chromosome 6.

HLA: human leukocyte antigens which act as transplantation ("histocompatibility") antigens.

ischemic time: the time elapsed between the clamping of the donor blood supply and the restoration of blood supply in the new host. This time can be divided into the cold ischemic time (when the graft is preserved at about 4° to 7°C.) and the warm ischemic time, when the graft is at or near body temperature.

prednisone: a cortisone derivative, which has moderate immunosuppressive and anti-inflamatory effects.

T cells: lymphocytes which mature in the thymus, and which are the principal cell mediating acute rejection.

AN INTRODUCTION TO TRANSPLANTATION CONCEPTS AND TERMS

Transplantation is the transfer of tissues from one site to another. This can be from one site to another in the same individual (autotransplantation). Alternatively, it can be between two individuals. If the donor of the tissus and the recipient of the tissue are genetically identical, this is know as an isograft. If they are genetically not identical, this is know either as an allograft (if the donor and recipient are from the same species) or an xenograft (if the donor and recipient are of different species). There are two types of problems with transplantation: surgical and immunologic. Surgical problems are organ-specific and primarily occur during the acute phase. The immunologic problems are called rejection and occur only in allografts and xenografts. Virtually all clinical organ transplantation involves allografts.

The genetic relationship between the donor and the recipient determines whether the tissues will be rejected. In general, the laws of transplantation state that

1. autografts or isografts are accepted.

2. allografts or xenografts are rejected.

3. the structures (antigens) which determine whether grafts are accepted are inherited in an dominant or co-dominant manner.

Rejection is an immunologic attack by the host cells against the donor tissue. The host cells recognize structures on the donor which distinguish the donor tissues from those of the host. These structures are know as transplantation antigens or histocompatibility antigens. In allografting, the strongest transplantation antigens are called the major histocompatibility antigens, which in man are the HLA antigens. They are controlled by the genes

of the major histocompatibility complex (or MHC), which in man is called the HLA complex. The genes ofthe HLA complex are located in chromosome 6.

The immune process in rejection is mediated by the lymphocytes of the host. Lymphocytes are of two types: B cells and T cells. B cells make antibody; T cells are responsible for cell mediated immunity and for regulation of the response. T cells are of two types: T4 cells, sometimes called the helper cells, and T8 cells, sometimes called the cytotoxic/suppressor cells. The helper T cells are important in helping the B cells to make antibody.

Rejection is of several types: acute, hyperacute, and chronic. Acute rejection usually occurs around the end of the first week but can occur at any time in the first several months. Acute rejection consists of 1) invasion of the graft by T lymphocytes, B lymphocytes, and macrophages, coupled with swelling of the graft (edema); 2) damage to the small blood vessels; 3) deterioration in graft function; and 4) rapidly progressing failure of the graft which may proceed to death of the entire graft (necrosis). Acute rejection usually proceeds from its initiation to its completion over a period of a few days but can be more rapid.

Acute rejection is believed to be mediated by the direct effects of T4 and possibly T8 cells, much of which is through the process called delayed type hypersensitivity. In this process, the T cells release mediators which damage the graft and organize inflammation. Thus other cells such as macrophages become activated and release mediators which further damage the graft. Antibody is formed during acute rejection and may play a role in the injury to the blood vessels. Hyperacute rejection, as mentioned above, is mediated by preformed antibody.

Hyperacute rejection occurs when the recipient is already immunized to the antigens of the donor before the transplant. In particular, the recipient has made cytotoxic antibody against the donor.

Hyperacute rejection is a fulminant process which can occur even on the operating table or within twelve hours. Hyperacute rejection occurs mainly with certain organs, such as kidney, and is unknown or infrequent with some other organs such as liver or heart/lung transplants.

Chronic rejection is an insiduous process, usually beginning after months or years, which proceeds to total destruction of the graft over a long period. The destruction is characterized by slow development of fibrous tissue, or the slow or direct effects of T cells. Chronic rejection is mediated by unknown mechanisms, probably involving antibody and T cell mediated immunity.

Diagnosis of Rejection

The cornerstone of the diagnosis of rejection is a deterioration in graft function or morphology. Function is followed by measuring biochemistry (such as serum creatinine in renal transplantation) and by following imaging such as nuclear medicine scanning to detect altered function. Changes in graft morphology are detected by ultrasound, cytology, or histology.

Although rejection is an immunologic process, it is not at present possible to reliably measure that process. This is partly because the process is so complex and ill-understood. Many immunologic tests are available to "monitor" the rejection of the graft; none is of proven value in detecting rejection in a maner which improves graft survival. Virtually all immunologic tests used for monitoring are relatively expensive, and all should be regarded as experimental. There is no need for a high level immunologic laboratory to support a clinical transplantation program, with the exception of the tissue typing and cross-matching facilities. However, ongoing research into the mechanism of rejection and the mechanisms of action of immunosuppressive drugs is clearly needed, and every unit

should regard itself as having a mandate to pursue such questions if the personnel are available.

Prevention of Rejection

As stated above, the laws of transplantation indicate that allografts must reject. In humans, virtually all transplants involving large organs must be allografts. Therefore strategies to avoid rejection must be employed. These include:

1. matching donor and recipient antigens

2. pretreating the donor before transplantation.

3. pretreating the recipient before transplantation.

4. treating the recipient after transplantation, to either prevent or reverse rejection.

1. Donor and Recipient Matching for HLA Antigens

Tissue typing consists of the identification of HLA antigens. It is based on a serologic test: HLA antigens of the donor and the recipient are identified by panels of antibodies, each directed against one HLA antigen. Using the complement dependent lysis test, these antibodies identify which antigens the individual possesses. Therefore, a donor organ can be put into a recipient who is found to match his/her antigens. It all HLA antigens are identical between the donor and recipient, graft survival is greatly improved. In practice, this only occurs with HLA identical siblings.

However, some degree of matching does help: in the case of parents and children, grafts can be exchanged because half identity will exist and this gives better graft survival than complete non-identity. Even among unrelated individuals, identifying and matching HLA antigens produces some effect on graft survival, although this effect is not strong and good graft survival can still be obtained when the tissues are completely mismatched.

Matching of donor antigens to recipient antigens should be distinguished from cross-matching, which consists of testing the recipient's serum for the presence of antibody against the donor. A positive cross-matching indicates that the recipient has antibody against the donor, and that hyperacute rejection is possible or likely. Donor recipient HLA matching is optional in many forms of transplantation. However, in kidney transplantation cross-matching of recipient serum against donor cells is mandatory.

2. Donor Pre-Treatment

The tissues of the donor are not uniformly strong in eliciting; some cells are much more capable of triggering rejection by recipient cells than others. Donor pre-treatment aims at eliminating such cells. The strategies have included a) culture of the donor organ to allow the donor cells which trigger strong rejection episodes (the passenger leukocytes) to die; b) donor pre-treatment with cytotoxic drugs, such as cyclosphosphamide, prednisone, or antilymphocyte globulin, to kill off the passenger leukocytes.

In general, donor pre-treatment for most tissues is either not feasible or does not significantly affect graft survival.

3. Pre-Treatment of the Recipient Before Transplantation

It was found empirically that recipients who receive blood transfusions two weeks or more before renal transplantation have an improved graft survival. This has permitted clinicians doing kidney transplantation to transfuse all recipients, and has cut kidney graft loss by 25 per cent or more in many series. Blood transfusion is one reason for recent improvement in graft survival. The blood transfusion effect only works before the first transplant, however, and has no effect if the person has already had a transplant which has been rejected.

Blood transfusion has not yet been extensively evaluated for its effect in prolonging graft survival in recipients of non-renal organs, but many suspect that such an effect would exist. The problem with blood transfusion is that it can induce the presence of antibodies in a few individuals, which can give positive cross-matches and therefore prevent the person from receiving certain grafts. This could be a problem in non-renal organs, where availability of a donor at a particular time is crucial.

In kidney transplantation, where living related donors are used, it has been found that donor specific transfusions can improve graft survival. In other words, the transfusions are taken, not from unrelated individuals from the blood bank, but from the donor. Three donor blood transfusions significantly improve the chances that a renal transplant from that donor will survive, provided they are given at least two weeks before the transplant. In practice, donor specific transfusions are used for kidney transplants from partially HLA identical relatives.

4. Recipients Immune Suppression

a. For prevention of rejection

Several drugs are used routinely for prevention of rejection: prednisone, cyclosporine, azathioprine, and, on an experimental basis, azathioprine plus cyclosporine:

i) Prednisone - this is a derivative or cortisol, an adrenal hormone. It has many effects on the immune system, including effects on cell traffic, on the release of enzymes from inflammatory cells, on stabilization of membranes, and, to some extent, a lytic effect on lymphocytes. It also impairs the release of important lymphocyte mediators, called interleukins 1 and 2 (IT-1 and IL-2). Its side effects are cataracts, diabetes, deterioration of joints and osteoporosis or loss of bone mineral. Excessive prednisone produces characteristic changes in

the appearance know as Cushing's Syndrome, characterized by a moon face, acne, weight gain or frank obesity and other features.

ii) Azathioprine - this is a drug related to the types of drugs used for treating cancer, called cytotoxic drugs. Azathioprine acts by impairing cell division, particularly in the bone marrow. In some individuals it can cause liver injury, but this is uncommon. The principal side effects are depression of white cells and platelets. In some individuals who do not tolerate azathioprine, the cytotoxic drug cyclophosphamide is used, but this is usually more toxic.

iii) Cyclosporine - this is a new drug which has increased graft survival considerably. It has been show in clinical trials to be significantly better than azathioprine, although severe rejection can still occur in some cases. It is a relatively safe drug, but must be handled very carefully and blood levels must be followed. Its principal side effect is damage to the kidney, which is partly reversible but partly irreversible with long treatment. It is costly, in the order of $5000 per patient per year, with treatment required indefinitely.

iv) Cyclosporine plus azathiorine. This combination therapy is being evaluated experimentally to determine its safety and efficacy. Generally, it has the possibility of decreasing the incidence of rejections on cyclosporine, while avoiding some side effects by allowing the patient to receive smaller doses of each drug than if the patient were on either drug alone. Cyclosporine and methotrexate (or other immunosuppressives) are being combined in experimental protocols in some units, particularly in bone marrow transplantation.

b To Reverse Rejection Episodes

i) Methylprednisolone (Solumedrol): This drug is given intravenously to treat acute rejection episodes. It is usually given on several consecutive days. It is generally effective in reversing rejection episodes, although probably less effective than the strategies listed below. Because it is a close relative of prednisone, the side effects are the same as those listed for prednisone. In some cases, high doses of oral prednisone are used instead of Solumedrol.

ii) Antilymphocyte Globulin (ALG): There are several closely related products available for treating rejection which are based on antibodies made in another species against human lymphocytes. These are know as antilymphocyte globulin, antithymocyte globulin, and rabbit antithymocyte serum. They are made by injection human lymphocytes into animals and then collecting the antibodies which those animals make. They are used by infusing these antibodies (xenoantibodies) into the person who is undergoing a rejection episode. They are highly effective in reversing rejection episodes in most cases. These treatments tend to be very expensive, but are used only for a very short period of time.

In many units, one of these preparations is also used for a short period of time to prevent rejection during the early post-operative period. Such prophylactic use may be able to circumvent some of the early problems with the use of cyclosporine and permit better renal function to be established before high levels of cyclosporine must be used.

iii) Monoclonal Antibodies against T Cell Antigens: Monoclonal antibodies are antibodies made by immortalized B cells which have been cloned so that every cell produces identical antibodies. Such antibodies tend to be both pure and powerful. One antibody against the T3 component of T cells has been shown to be

highly effective in reversing rejection episodes. Anti T3 antibodies may be an alternative to ALG for severe rejection episodes, but their relative efficacy, cost, and safety are unknown.

iv) Other Treatments for Rejection: Certain strategies for treating rejection have a less well-defined role, including plasmapheresis, leukopheresis, and graft irradiation. Certain centers continue to evaluate total lymphoid irradiation or thoracic duct drainage on an experimental basic for transplant immunosuppression.

The Monitoring of Cyclosporine Levels

A laboratory for monitoring cyclosporine plasma of blood levels should be available to every transplant center, although one laboratory can serve several centers. Indeed, it is advisable to centralize this to some extent because the expenses of the radioimmune assay can be reduced by batching. The radioimmune assay is based on a kit produced by the Sandoz drug company. Most units in Canada rely on monitoring of plasma or serum levels, although some units elsewhere use whole blood monitoring.

In general, the cyclosporine levels should be available at least five days a week, during the acute transplantation period and in some cases six or seven days a week. The turnaround time for a specimen drawn in the morning should only be a few hours. Specimens can be sent by mail or courier, so that the laboratory can monitor patients at considerable distance. The cyclosporine results for the day should be monitored by the transplant coordinator, who will refer the abnormal results to the appropriate clinician.

In certain circumstances, particularly in the presence of liver disease or in liver transplantation, it may be advisable to have high pressure liquid chromatography (HPLC) monotoring available.

Unfortunately, such samples cannot be batched, and HPLC is not a suitable alternative for radioimmune assay.

In general, cyclosporine monitoring can be undertaken by the same facilities available for monitoring other drugs by radioimmune assay, and in some cases may be combined whith the radioimmune assays for protein hormones. It is advisable to have an experienced clinical biochemist available to the cyclosporine monitoring laboratory.

ORGAN PRESERVATION

1. Kidney Preservation

The main principles of kidney preservation for transplantation are:

i) to preserve function in the donor by ensuring renal perfusion.

ii) to establish a diureses during the donor nephrectomy, prior to clamping the vessels.

iii) to keep the warm ischemic time as short as possible.

iv) after removal of the kidney, to obtain core cooling with an appropriate flush solution. The current flush solutions are Collins and euro Collins which have high potassium and low sodium, to prevent cell swelling.

Pulsatile perfusion by machine uses a fluid with some plasma proteins and an extra-cellular fluid-like electrolyte solution. This procedure has been claimed to improve renal function. In fact, it is not clear that it does so. The current trend is against pulsatile perfusion, because its additional expenditure is difficult to justify by the small increment in improved early function. However, this issue remains contentious.

The principal method of renal perfusion is by simple cold storage, in which the flushed, cooled kidney is stored in a slush of a electrolyte containing fluid at about 4 °C. This is suitable for up to 48 - 72 hours, but even within this period early function probably declines as preservation time increases. It remains desirable to keep the preservation time as short as is compatible with optimal recipient selection and preparation.

2. Heart Preservation

Preservation of the heart for transplantation requires pre-operative, operative and post-operative considerations.

i) Pre-Operative

Superb medical management of the donor's circulatory blood volume, inotropic and chronotropic status, acid base and biochemical status, and peripheral vascular resistance is necessary to avoid the 20 per cent loss of potentially suitable heart donors due to medical mismanagement.

Protocols for the pre-operative management of donors for cardiac transplantation provided optimal physiological support of all organ systems.

ii) Intra-operative

The heart may be "ischemically preserved" using a combination of hypothermic perfusion and topical immersion cooling for up to five hours. Following implantation, excellent cardiac function is expected.

Although longer preservation intervals have been obtained experimentally with both single flush perfusion and continuous perfusion techniques, these strategies have not provided sufficiently reproducible heart preservation to be clinically applicable.

Once the heart has been satisfactorily cooled to approximately 4 degrees C, it is excised and immersed in normal saline at 4 degree C. The heart may be then immediately transplanted, or transported in special containers which are immersed in ice, for implantation at the distant recipient center within an ischemic time period of five hours.

3. Heart/Lung Preservation

Preservation of both the heart and lungs for transplantation requires pre-operative, operative and post-operative considerations.

i) Pre-operative

Superb medical management is required to ensure optimal cardiac and pulmonary function prior to organ removal.

ii) Operative

The heart and lungs may be preserved using any one of two acceptable techniques.

The first method is similar to that for the preservation of the heart alone, in which the heart is perfusion cooled with a single bolus of 10 ml.kg of cardioplegic solution and a topical balance salt solution, and the lungs are perfusion cooled with a single bolus of 20 ml/kg of modified Collins II solution, plus topical immersion cooling with 4 degree C balanced salt solution.

The heart and lungs, which have been cooled to approximately 4 degrees C, are then removed with the lungs approximately three-quarters inflated.

The second technique, which has some technical advantage in terms of the actual harvesting of the heart/lung access, takes advantage of cooling the heart and lungs with cardiopulmonary bypass, with final single bolus flush perfusion of the heat with cardioplegia. No electrolyte solution is perfused through the pulmonary vascular bed. This latter technique has the advantage of cooling the lungs through both the bronchial arterial circulation as well as via the pulmonary arterial bed.

iii) Post-operative

Once the heart and lungs have been cooled and removed from the donor's thorax, with the lungs partly inflated, the entire specimen is placed in a balanced salt solution at 4 degrees C within two large protective plastic bowel bags, each of which has 4 degree C balanced salt solution with it. The two plastic bags with the contained organs are then placed into a large stiff walled protective container,

which also contains 4 degree C balanced salt solution, and the entire contents are placed into a large ice chest for transportation to the recipient center.

The acceptable ischemic time for the heart is up to five hours and for the lungs is up to four hours.

If the donor and recipient are in the adjacent operating theatres, then it is unnecessary to package the heart and lungs in this fashion; rather, the organs may simply be implanted in the recipient.

4. Lung Preservation

Preservation of the lung alone, for transplantation requires pre-operative, operative and post-operative considerations.

i) Diligent donor management with particular attention to pulmonary toilet and physiotherapy, are required to ensure satisfactory lung function following transplantation.

ii) Intra-operative

The lung may be preserved as described above for heart/lung preservation.

iii) Post-operative

If the lung is not immediately implanted, it may be packaged and transported as described above for the combined heart/lung "bloc".

5. Bone Marrow Preservation

See Section 3, item (g) of the Guidelines on Bone Marrow Transplantation, page 45.

SPECIAL POLICIES RELATED TO TRANSPLANTATION

The specific special policies related to organ transplantation that must be developed include:

1. Current indications and contraindications for transplantation.

2. Guidelines for the referring physician.

3. Guidelines for social work referrals.

4. Financial requirements of the patient.

5. Referral evaluation worksheet for the referring center.

6. Recipient evaluation at the referring center.

    6.1 Initial evaluation.
    6.2 After acceptance as a transplant candidate or if acceptance appears likely.
    6.3 Supplementary evaluation for transplantation candidates as applicable

7. Protocol for the pre-operative management of donors for organ transplantation.

8. Data record for organ transplantation donors.

9. Personnel coordination for transplantation.

10. Transfer of responsibility between medical specialties for pre-operative, peri-operative and post-operative care.

11. Pre- and post-operative orders.

    11.1 Final transplantation recipient evaluation
    11.2 Pre-operative orders for organtransplantation recipients.

11.3 Organ transplantation: immediate post-operative orders.
11.4 Organ transplantation: post extubation orders.
11.5 Organ transplantation: transfer orders.
11.6 Donor orders.
11.7 Out-patient management guidelines.

12. Example consent forms.

12.1 Consent of recipient for transplantation.
12.2 Consent to the use of investigational drugs.
12.3 Consent for autopsy.

13. Procedure for decontamination of an organ transplantation patient room.

14. Procedure for India ink tatooing for V1 and V6 ECG leads.

Additional General policies appear in Annex D.

ANNEX D

ADMINISTRATIVE ORGANIZATION, POLICIES AND PROCEDURES

Guidelines for the administrative organization, policies and procedures for units/services/programs (hereinafter referred to as program(s) in hospitals were formulated after a review of provincial, national and international information. It is hoped that the following outline will serve as a guide for the development of more comprehensive and specific program policies in order to ensure the most effective and efficient delivery of patient care in these programs.

I. ROLE AND OBJECTIVES

- Role and objectives of programs in hospitals

- Type of patient served

  - by diagnosis and/or severity of illness
  - restriction of service, if any (eg. terminally-ill patients)

- Components of program provided

II. ORGANIZATION OF PROGRAM

- Governing Board responsibility

- Relationship to Administrator and Medical Staff

- Service Management

(i) Specific responsibilities of staff
  - Medical Director
  - Other medical Staff
  - Direct Patient Care staff
  - Other staff (Administrative, Technical and other)

(ii) Committees

- Membership to be defined by discipline and number
- Terms of reference to be defined
- Provision for consultation with appropriate hospital and medical staff
- Schedules for formal and ad hoc meetings

III. POLICIES FOR OPERATION OF PROGRAM

1. General

- Admission authority (Identification of individual(s) who have authority to admit)

- Admission priorities:

  - Clinical condition
  - Diagnostic category

- Discharge policies and planning

- Drug and procedure (new) approval process

- Emergency delegation of responsibility to medical, nursing and/or other staff

- Ethics processes

- Handling of emergency situations including C.P.R.

- Infection control and isolation

- Lenght of stay by diagnosis

- Medical Orders

- Palliative care, determination of death, authorization for autopsies, handling of bodies

- Patient records, reports and charting

- Referral, consultation (mandatory and other), transfer, follow-up

- Research/clinical investigation

- Routine admission Standing Orders

- Utilization monitoring

2. **Staff**

- Criteria for granting medical/clinical privileges

- Delineation of student and supervisor roles including responsibility, authority and accountability

- Medical coverahe/Staff coverage of service

- Orientation and continuing education

- Performance evaluation

- Position descriptions

- Selection criteria: education, experience, interests

- Volunteers

3. **Patient**

- Confidentiality

- Consent for treatment

- Family participation

- Patient/family education

- Patient's rights

- Patient valuables, assets and belongings

- Visiting privileges

4. Safety

- Equipment maintenance and safety

- Fire/disaster plans and associated isolation procedures

- Missing patient search procedures and risk identification

- Reporting of accidents and incidents

- Safety and accident prevention

- Use of restraints

5. Quality Assurance

- Audits: medical and nursing care, concurrent and retrospective

- Continuing evaluation of effectiveness of service

- Employee performance appraisal

- Incident reports

- Infection control

- Morbidity/mortality review

- Patient care review

- Patient status assessment on admission and discharge

- Peer review

- Practice standards

- Product and equipment use and evaluation

IV. PROCEDURES

1. Elective procedures: medical, nursing and other

2. Emergency alert system procedures

3. Medical record and statistical procedures

4. Policy and procedure manuals

GUIDELINES FOR INSTITUTIONAL PROGRAMS

The following guidelines have been prepared by the federal-provincial Subcommittee on Institutional Programs Guidelines. These guidelines were requested by the Federal-Provincial Advisory Committee on Institutional and Medical Care Services. Some guidelines previously published by the Subcommittee.

Addiction Services
Adult Long Term Institutional Care
Adult Psychiatric Services Provided by General Hospitals
Breast Imaging Services: Mammography
Burn Unit
Cardiovascular Services in Hospitals
Child and Adolescent Services in General Hospital
Child and Youth Long Term Services
Computed Tomography
Day Medicine
Day Surgery Unit
Dental Care Units in Hospitals
Diabetic Day Care Unit
Diagnostic Imaging Services and Systems, An Overview
Diagnostic Ultrasound Facilities in Hospitals
Emergency Services in Hospitals
End-Stage Renal Disease Program
Geriatric Day Hospitals
Geriatric Unit in a Hospital
Intensive Care Unit
Magnetic Resonance Imaging Services
Nuclear Medicine in Hospitals
Organ and tissue Donation Services in Hospitals
Palliative Care Services in Hospitals
Patient Hostel Unit
Perinatal Intensive Care Units in a Perinatal Care Network
Pre-Hospital Emergency Services
Pulmonary Function Laboratories

Rehabilitation Medicine Program
Respiratory Therapy Program
Spinal Cord Injury Program
Stroke Services
Vital Organ Transplant Centres